EXHIBIT A

Lee E. Kirsch
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April 2013

EDUCATION AND PROFESSIONAL HISTORY

Education

Ph D, Pharmaceutics, 1982
The Ohio State University

BS, Pharmacy, 1975
Purdue University

Professional and Academic Positions

Professor, The University of Iowa, August 2010 - Present, Division of Pharmaceutics (Primary Appointment), Department of Chemical and Biochemical Engineering (Secondary Appointment), and International Programs (Secondary Appointment: June 2014 – Present).
Visiting Professor, Mahidol Univesity, Faculty of Pharmacy, Thailand (January, 2014 – April, 2014)
Professor, Virginia Commonwealth University, Department of Pharmaceutics (Affiliate Appointment). (May 2005 - Present).
Adjunct Professor, Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand (2003 – present)
Associate Professor, The University of Iowa, College of Pharmacy. (November 1994 - July 2010).
Associate Professor, The University of Iowa, Department of Chemical and Biochemical Engineering (Secondary Appointment). (May 2006 - July 2010).
Senior Research Scientist/group leader, Lilly Research Laboratories. (January 1992 - November 1994).
Research Scientist/group leader, Lilly Research Laboratories. (January 1987 - January 1992).
Senior Pharmaceutical Chemist, Lilly Research Laboratories. (November 1982 - January 1987).
Research Associate, The Ohio State University. (June 1979 - November 1982).
Teaching Assistant, The Ohio State University. (August 1978 - June 1979).
Community Pharmacist, Family Pharmacy North Bloomington, Indiana. (July 1975 - August 1978).

Honors and Recognition

Editor-in-chief, AAPS PharmSciTech Journal. (July 2008 – December, 2014).
Fellow of the American Association of Pharmaceutical Scientists (June 2013)
Distinguished Service Award, Parenteral Drug Association. (February 2011).
Editor, PDA Journal of Pharmaceutical Science and Technology. (July 2000 - June 2008).
Fred Simon Award for best paper, PDA Journal of Pharmaceutical Science and Technology. (October 1997).
Jack L. Beal Postbaccalaureate Award, The Ohio State University College of Pharmacy. (May 1997).

TEACHING AT THE UNIVERSITY OF IOWA AND EXTERNAL TEACHING: INTERNATIONAL AND US

Professional PharmD Courses
Pharmacokinetics and Biopharmaceutics, Pharmacy 46:138, 2002-2009
Pharmaceutical Proteins unit in Pharmacy 46:123, 2002-2013
Advanced Compounding, Pharmacy 46:120, 2004-2005
Drug Stability in Pharmacy 46:123 and 46:124, 2005-2013, 1995-2000
Fundamentals of Kinetics in Pharmacy 46:123, 46:050, 2005-2013
Fundamentals of Pharmacokinetics in Pharmacy 46:124, 2010-2013
Solids processing, Packaging, Capsules, Lyophilized Powders units in Pharmacy 46:124, 1995-2000

Graduate Courses in Pharmaceutics
Pharmacy Research, Pharmacy 46:233, 1995-2015
Pharmaceutical Product Development, Pharmacy 46: 225, 1999 and 2006
Drug Degradation Kinetics and Mechanisms (Drug Stability) 46:206, 1995, 1997, 1999, 2001, 2003, 2007, 2009, 2011, 2013

External Teaching: International and US
Pharmaceutical Package Integrity, PDA Research and Training Center, 1998
Drug Degradation Kinetics Short Course, Chulalongkorn University, International Pharmaceutical Technology Graduate Program, 2002, 2003, 2005, 2008, 2009, 2010, 2011, 2012, 2013, 2014 Bangkok, Thailand
Drug Degradation Kinetics Short Course, Virginia Commonwealth University, Pharmaceutical Sciences Graduate Program, 2005
Drug Degradation Kinetics Short Course, Mahidol University, Bangkok, Pharmaceutical Sciences Graduate Program, 2014
Chaired working group to evaluate the concept of an intercollegiate undergraduate degree in pharmaceutical engineering and science
Chaired the education committee for NIPTE working on the design of a national curriculum in pharmaceutical technology

M.S. Students Directed
Craig Moeckly (Non-thesis) degree conferred 1997
Walasiri Muangsiri (Thesis) degree conferred July, 2000

Simei Li (Non-thesis) degree conferred December, 2000
Bhanu Kalvakota (Non-thesis) degree conferred December, 2002
Pipat Sittisak (Thesis) with W. Muangsiri, Chulalongkorn University, degree conferred 2010

Ph.D. Students Directed
Young-Sihn Sihn, degree conferred June 1997
Lida Nguyen, degree conferred December, 2001
Xiaoguang Zhang, degree conferred December, 2001
Anjali Joshi, degree conferred December, 2001
Walasiri Muangsiri, degree conferred December, 2003
Madhushree Gokhale, degree conferred May, 2006
Himanshu Naik (with L. Fleckenstein), degree conferred December, 2007
Boontarika Chanvorachote (with W. Muangsiri), degree conferred June, 2009 (Chulalongkorn Univeristy)
Salil Desai degree conferred December, 2009
Zhixin Zong degree conferred May, 2012
Jiang Qui, degree conferred May, 2013
Hong Guann Lee (with D. Flanagan), degree conferred May, 2015
Nguyen Quynh Hoa, degree conferred December, 2014
Radaduen Tinmanee, degree anticipated May, 2015
Mo'tasem Mohamed Alsmadi (with L. Fleckenstein), degree conferred December, 2014
Phawanan Sawangchan, pre-comprehensive
Pratak Ngeacharernkul pre-comprehensive
Éverton do Nascimento Alencar, visiting Ph.D. scholar from Federal University of Rio Grande do Norte, Natal, Brazil, 2014-2015

Post-doctoral Scholars
Gisela N. Piccirilli, Ph.D., 2011
Stephen Stamatis, Ph.D., 2011-2013
Eiji Ueyama, Ph.D., 2013-2014

SCHOLARSHIP/RESEARCH/PROFESSIONAL PRODUCTIVITY

Publications

1. Salil Dileep Desai and Lee E. Kirsch The Ortho Effect on the Acidic and Alkaline Hydrolysis of Substituted Formanilides, submitted to *International Journal of Chemical Kinetics*, February, 2015.
2. Hoa Q. Nguyen, Stephen D. Stamatis, Lee E. Kirsch, A novel method for assessing drug degradation product safety using physiologically-based pharmacokinetic models and stochastic risk assessment, accepted for publication *Journal of Pharmaceutical Science,* 2015
3. Boontarika Chanvorachote, Jiang Qiu, Walaisiri Muangsiri, Ubonthip Nimmannit, and Lee E. Kirsch (2015) The interaction mechanism between lipopeptide (daptomycin) and polyamidoamine (PAMAM) dendrimers , *Journal of Peptide Science*, DOI: 10.1002/psc.2752.
4. Qiu, J. and Kirsch, Lee E. (2014) Evaluation of Lipopeptide (Daptomycin) Aggregation Using Fluorescence, Light Scattering, and Nuclear Magnetic Resonance Spectroscopy,

Journal of Pharmaceutical Sciences, 103(3), 853–861.

5. Dempah KE, Barich DH, Kaushal AM, Zong Z, Desai SD, Suryanaranyanan R.; Kirsch L, Munson EJ; (2013) Investigation Gabapentin Polymorphism Using Solid-State NMR Spectrocsopy; *AAPS PharmSciTech*, 14(1), 19-28.
6. Zong, Z., Qiu, J., Tinamnee, R., Kirsch, L. E. (2012). Kinetic model for solid-state degradation of gabapentin. *Journal of Pharmaceutical Science, 101*(6), 2123-2133.
7. Zong, Z., Kirsch, L. E. (2012). Studies on the Instability of Chlorhexidine, Part 1. *Journal of Pharmaceutical Science, 101*(7), 2417-2427.
8. Mockus, L., Lainez, J., Reklaitis, G., Kirsch, L. E. (2011). A Bayesian Approach to Pharmaceutical Product Quality Risk Quantification. *Informatica, 22*(4), 537-558.
9. Qiu, J., Yu, L., Kirsch, L. E. (2011). Estimated pKa values for specific amino acid residues in daptomycin. *Journal of Pharmaceutical Science, 100*(10), 4225-4233.
10. Ratcliff, J. L., Kirsch, L. E., Dykstra, J. W., Cooley, W. E. (2011). Fluoride and chlorine dioxide-containing compositions and method for reducing demineralization of teeth. *PCT Int. Appl*, WO 2010075419 A1 20100701.
11. Zong, Z., Desai, S., Barich, A., Huang, H.-S., Munson, E., Suryanarayanan, R., Kirsch, L. E. (2011). The Stabilizing Effect of Moisture on the Solid-State Degradation of Gabapentin. *AAPS PharmSciTech, 12*(3), 924-931.
12. Chanvorachote, B., Nimmannit, U., Muangsiri, W., Kirsch, L. E. (2009). An Evaluation of a Fluorometric Method for Determining Binding Parameters of Drug–Carrier Complexes Using Mathematical Models Based on Total Drug Concentration. *Journal of Fluorescence, 19*(4), 747-753.
13. Gokhale, M., Kearney, W., Kirsch, L. E. (2009). Glycosylation of Aromatic Amines I: Characterization of the Reaction Products of Kynurenine and Glucose in Aqueous Solutions. *AAPS PharmSciTech, 10*(2), 317-328.
14. Tan, B., Naik, H., Jang, I.-J., Yu, K.-S., Kirsch, L. E., Shin, C.-S., Fleckenstein, L. (2009). Population Pharmacokinetics of Artesunate and Dihydroartemisinin Following Single- and Multiple-Dosing of Oral Artesunate in Healthy Subjects. *Malaria Journal, 8*(1), 304.
15. Gokhale, M., Kirsch, L. E. (2009). Glycosylation of aromatic amines II: Kinetics and mechanisms of the hydrolytic reaction between kynurenine and glucose. *Journal of Pharmaceutical Science*, DOI 10.1002/jps.21754.
16. Gokhale, M., Kirsch, L. E. (2009). Glycosylation of aromatic amines III: Mechanistic implications of the pH-dependent glycosylation of various aromatic amines (kynurenine, 2'-aminoacetophenone, daptomycin, and sulfamethoxzaole). *Journal of Pharmaceutical Science*, DOI 10.1002/jps.21765.
17. Kirsch, L. E. (2008). On Transforming Pharmaceutical Technology Education. http://www.pharmamanufacturing.com/articles/2008/113.html
18. Hoppe, C. C., Nguyen, L. T., Kirsch, L. E., Wiencek, J. M. (2008). Characterization of seed nuclei in glucagon aggregation using light scattering methods and field-flow fractionation. *Journal of Biological Engineering, 2*(10).
19. Kirsch, L. E. (2007). Package Integrity Testing. *CRC Press*.
20. Muangsiri, W., Kirsch, L. E. (2006). The Protein-binding and Drug Release Properties of Macromolecular Conjugates containing Daptomycin and Dextran. *International Journal of Pharmaceutics, 315*, 30-43.
21. Naik, H., Murry, D. J., Kirsch, L. E., Fleckenstein, L. (2005). Development and validation of a high-performance liquid chromatography-mass spectroscopy assay for determination of artesunate and its metabolite dihydroartemisinin in human plasma. *Journal of Chromatography B, 816*(1-2), 233-242.

22. Kirsch, L. E. (2005). Extemporaneous Quality. *PDA Journal of Pharmaceutical Science and Technology, 59*(1 & 3).
23. Joshi, A., Kearney, W., Sawai, M., Kirsch, L. E. (2005). Studies on the Mechanism of Aspartic Acid Cleavage and Deamidation in the Acidic Degradation of Glucagon. *Journal of Pharmaceutical Sciences, 94*(9), 1912-1927.
24. Muangsiri, W., Kearney, W. R., Teesch, L. M., Kirsch, L. E. (2005). Studies on the Reactions between Daptomycin and Glyceraldehyde. *International Journal of Pharmaceutics, 289*(1-2), 133-150.
25. Zhang, X., Kirsch, L. E. (2004). Correlation of the Thermal Stability of Phospholipid-based Emulsions and Microviscosity Measurements as Determined by Fluorescence Polarization. *Pharmaceutical Development and Technology, 9*(2), 219-227.
26. Kirsch, L. E. (2004). Lessons unlearned. *PDA Journal of Pharmaceutical Science and Technology, 58*(3), 119-120.
27. Kirsch, L. E. (2004). PDA Students. *PDA Journal of Pharmaceutical Science and Technology, 58*(5), 241-242.
28. Joshi, A., Kirsch, L. E. (2004). The estimation of glutaminyl deamidation and aspartyl cleavage rates in glucagon. *International Journal of Pharmaceutics, 273*(1-2), 213-219.
29. Zhang, X., Kirsch, L. E. (2003). An Assessment of Techniques for Evaluating the Physical Stability of Parenteral Emulsions. *PDA Journal of Pharmaceutical Science and Technology, 57*(4), 300-315.
30. Nguyen, L., Wiencek, J., Kirsch, L. E. (2003). Characterization Methods for the Physical Stability of Biopharmaceuticals. *PDA Journal of Pharmaceutical Science and Technology, 57*(6), 429-445.
31. Zhang, X., Kirsch, L. E. (2003). The Physical Stability of Thermally-stressed Phospholipid-based Emulsions Containing Methyl, Propyl and Heptyl Parabens as Model Drugs. *International Journal of Pharmaceutics, 265*(1-2), 133-140.
32. Kirsch, L. E. (2002). Beyond bioterrorism. *PDA Journal of Pharmaceutical Science and Technology, 56*(3), 113-114.
33. Joshi, A., Kirsch, L. E. (2002). The Relative Rates of Asparaginyl and Glutaminyl in Glucagon Fragment 22-29 under Acidic Conditions. *Journal of Pharmaceutical Science, 91*(11), 2332-2342.
34. Kirsch, L. E., Zhang, X., Muangsiri, W., Redmon, M., Luner, P., Tartrate, D. (2001). Development of a Lyophilized Formulation for (R,R)-Formoterol (L)-Tartrate. *Drug Development and Industrial Pharmacy, 27*(1), 89-96.
35. Kirsch, L. E. (2001). Power to the People. *PDA Journal of Pharmaceutical Science and Technology, 55*(5), 261-262.
36. Luner, P., Kirsch, L. E., Majuru, S., Oh, E., Joshi, A., Wurster, D., Redmon, M. (2001). Preformulation Studies on the S-isomer of Oxybutynin Hydrochloride, an Improved Chemical Entity (ICE). *Drug Development and Industrial Pharmacy, 27*(4), 321-329.
37. Kirsch, L. E. (2001). Research Misconduct. *PDA Journal of Pharmaceutical Science and Technology, 55*(4), 205-206.
38. Muangsiri, W., Kirsch, L. E. (2001). The Kinetics of Daptomycin Degradation in Alkaline Solutions. *Journal of Pharmaceutical Science, 90*(8), 1066-1075.
39. Kirsch, L. E. (2000). Peer Review Fallibility. *PDA Journal of Pharmaceutical Science and Technology, 54*(4), 279.
40. Kirsch, L. E. (2000). Pharmaceutical Container/Closure Integrity VI: Correlations Between Liquid Tracer Methods and Microbial Ingress. *PDA Journal of Pharmaceutical Science and Technology, 54*(4), 305.

41. Joshi, A., Kirsch, L. E. (2000). The Acidic Degradation Pathways of Glucagon. *International Journal of Pharmaceutics, 203*(1-2), 115.
42. Kirsch, L. E. (2000). The Ivied Halls of Industry. *PDA Journal of Pharmaceutical Science and Technology, 54*(6), 433-434.
43. Kirsch, L. E. (2000). The PDA Journal and the Validation of Science. *PDA Journal of Pharmaceutical Science and Technology, 54*(3), 171.
44. Kirsch, L. E. (2000). The Rule of Three. *PDA Journal of Pharmaceutical Science and Technology, 54*(5), 365.
45. Nguyen, L., Muangsiri, W., Kirsch, L. E., Schiere, R., Morton Guazzo, D. (1999). Pharmaceutical Container/Closure Integrity IV: Development of an Indirect Correlation Between Microbial Ingress and Vacuum Decay Leakage Detection. *PDA Journal of Pharmaceutical Science and Technology, 54*(4), 211.
46. Kirsch, L. E., Nguyen, L., Kirsch, A. M., Schmitt, G., Koch, M., Wertli, T., Lehmann, M., Schramm, G. (1999). Pharmaceutical Container/Closure Integrity V: Comparison of Helium Leak Rate and LFC Methods. *PDA Journal of Pharmaceutical Science and Technology, 53*(5), 235.
47. Carroll, M. C., Denny, V. F., Guazzo, D. M., Kaiser, M. W., Kirsch, L. E., Ludwig, J. D., Masover, G. K., May, J. L., Moldenhauer, J. E., Olsen, J. I., Polson, T. M., Wright, G. E. (1998). Technical Report No. 27: Pharmaceutical Package Integrity. *PDA Journal of Pharmaceutical Science and Technology, 52*(S2).
48. Kirsch, L. E., Nguyen, L., Moeckly, C. S. (1997). Pharmaceutical Container/Closure Integrity I: Mass Spectrometry-based Helium Leak Rate Detection for Rubber-stoppered Glass Vials. *PDA Journal of Pharmaceutical Science and Technology, 51*(5), 187.
49. Kirsch, L. E., Nguyen, L., Gerth, R. (1997). Pharmaceutical Container/Closure Integrity II: The Relationship Between Microbial Ingress and Helium Leak Rates in Rubber-stoppered Glass Vials. *PDA Journal of Pharmaceutical Science and Technology, 51*(5), 203.
50. Kirsch, L. E., Nguyen, L., Moeckly, C. S., Gerth, R. (1997). Pharmaceutical Container/Closure Integrity III: The Relationship Between Microbial Ingress and Helium Leak Rates in Rubber-stoppered Glass Vials. *PDA Journal of Pharmaceutical Science and Technology, 51*(5), 195.
51. Sihn, Y.-S., Guillory, J., Kirsch, L. E. (1997). Quantitation of Taurolidine Decomposition in Polymer Solutions by Chromotropic Acid Formaldehyde Assay Method. *Journal of Pharmaceutical and Biomedical Analysis, 16*(4), 643.
52. Kirsch, L. E., Sihn, Y.-S. (1997). The Effect of Polyvinylpyrrolidine on the Stability of Taurolidine. *Pharmaceutical Development and Technology, 2*(4), 345.
53. Kirsch, L. E., Nguyen, L., Moeckly, C. S., Gerth, R. (1996). The Application of Mass Spectrometry Leak Testing to Pharmaceutical Container/Closure Integrity. *Proceedings of the PDA International Congress*.
54. Kirsch, L. E., Riggin, R., Gearhart, D., LeFeber, D., Lytle, D. (1993). In-process Protein Degradation by Exposure to Trace Amounts of Sanitizing Agents. *Journal of Parenteral Science and Technology, 47*, 155.
55. Kirsch, L. E., Redmon, M. P. (1993). Quality Tools for Pharmaceutical Product Development. *Proceedings of the Biopharmaceuctical Section of the American Statistical Association*.
56. Inman, E. L., Kirsch, L. E. (1990). Stabilized parenteral formulation of daptomycin. *Eur. Pat.*.
57. Kirsch, L. E., Molloy, R., DeBono, M., Baker, P., Farid, K. (1989). Kinetics of the Aspartyl

Transpeptidation of Daptomycin, a Novel Lipopeptide Antibiotic. *Pharmaceutical Research, 6*, 387.
58. Kirsch, L. E., Notari, R. (1984). Aqueous Conversion Kinetics and Mechanisms of Ancitabine, Prodrug of the Antileukemic Agent Cytarabine. *Journal of Pharmaceutical Sciences, 73*, 897.
59. Kirsch, L. E., Notari, E. (1984). Pharmacokinetic Prodrug Modeling: In Vitro and In Vivo Kinetics and Mechanisms of Ancitabine Bioconversion to Cytarabine. *Journal of Pharmaceutical Sciences, 73*, 728.
60. Kirsch, L. E., Notari, R. (1984). Theoretical Basis for the Detection of General-Base Catalysis in the Presence of Predominating Hydroxide Catalysis. *Journal of Pharmaceutical Sciences, 73*, 724.
61. Larson, R., Kirsch, L. E., Shaw, S., Christian, J., Born, G. (1972). Excretion and Tissue Distribution of Uniformly Labeled 14C-Pentachlorophenol in Rats. *Journal of Pharmaceutical Sciences, 61*, 2004.

Presentations

1. Lee Kirsch, "Physiologically-based Pharmacokinetic Models and Tools for Drug Development and Therapeutics", February 21, 2014, Universiti Kebangsaa Malaysia, Kuala Lumpur, Malaysia.
2. Lee Kirsch, "Linking Stability to Manufacturing in the Quality-By-Design Pharmaceutical Development Paradigm", February 20, 2014, The University of Nottingham-Malaysia, Malaysia.
3. Lee E. Kirsch, "Trends in Pharmaceutical Sciences: Education and Research", February 28, 2014, University of Philippines-Manila, Philippines.
4. Lee E. Kirsch, "Drug Degradant Risk Assessment using PBPK Modeling", March 4, 2014, Mahidol University, Thailand.
5. Lee E. Kirsch, "Get Reader➔Get Set➔Publish: the why, what and how of science writing", March 11, 2014, Mahidol University, Thailand.
6. Lee E. Kirsch, "Modernized Pharmaceutical Stability Evaluation and Packaging Science". March 26, 2014, University of Surabaya, Indonesia.
7. Lee E. Kirsch, "On the Role of Physical Stability in the Chemical Instability of Pharmaceuticals". March 28, 2014, Institut Teknologi Bangdung, Indonesia.
8. Lee E. Kirsch, "Kinetics and Mechanisms of Gabapentin Instability", March 29, 2014, Universitas Gadjah Mada, Yogyakarta, Indonesia.
9. Lee E. Kirsch, "Trends in Pharmaceutical Technology Education", April 8, 2014, University of Health Sciences, Vientiane, Lao PDR.
10. Lee E. Kirsch, "Trends in Pharmaceutical Sciences, Manufacturing and Regulatory", Hanoi University of Pharmacy, April 5, 2014, Vietnam.
11. Lee E. Kirsch, "Physiologically-based Pharmacokinetic Models and Tools for Drug Development and Therapeutics Applications". SINATER 2013, Federal University of Pernambuco, Recife, Brazil, 2013.
12. Mo'tasem M. Alsmadi, Stephen D. Stamatis, Lawrence Fleckenstein, and Lee E. Kirsch, "Whole Body Physiologically Based Pharmacokinetic (WBPBPK) Model of Ivermectin (IVM)" 2013, *AAPS Annual Meeting and Exposition*. San Antonio, TX.
13. Nguyen HQ, Stamatis SD, Kirsch LE., "Risk assessment of drug degradants using a physiologically-based pharmacokinetic model approach". 2013, *AAPS Annual Meeting and Exposition*. San Antonio, TX.

14. Radaduen Tinmanee, Stephen D. Stamatis, Lee E. Kirsch, “Modeling Chemical and Physical Instability Pathways of Gabapentin/Excipient Mixtures”, 2013, *AAPS Annual Meeting and Exposition*. San Antonio, TX.
15. Nguyen HQ, Stamatis SD, Kirsch LE “Physiologically based risk assessment for drug product degradants with a case study for aniline in rat”.. 2012. *Health Sciences Research Week*. University of Iowa. Carver College of Medicine.
16. Radaduen Tinmanee, Stephen D. Stamatis, Lee E. Kirsch, Sarah C. Larsen, Kenneth R. Morris. “The Effect of Excipients on API Stability: Covalent and Polymorphic Transitions.” Poster session presented at: 2012 AAPS Annual Meeting and Exposition; 2012 October 14-18; Chicago, IL.
17. Stamatis SD, McLennan MJ, and Kirsch LE, “Architecture of pHUBpk: A portal to active learning environments for understanding rational linkages between drug and patient characteristics and pharmacokinetics”, AAPS, Chicago IL, 2012
18. Stamatis SD, McLennan MJ, and Kirsch LE, “Active learning environments for understanding drug distribution, elimination and bioequivalence in pHUBpk on the pharmaHUB”, AAPS, Chicago IL, 2012
19. Nguyen H, Stamatis SD, and Kirsch LE, “Risk Assessment of drug degradants using a physiologically-based Pharmacokinetic Model Approach”, AAPS Chicago IL, 2012
20. Stamatis SD, McLennan MJ, and Kirsch LE, “Kpred and Vdss: Free Tools on the PharmaHUB for Exploring Drug Tissue Partitioning and Distribution”, Podium presentation, AIChE National Meeting, Pittsburgh, PA, 2012
21. Tinmanee, R., Stamatis, S., Huang, H., Ngeacharernkul, P., Kirsch, L. E., AAPS Annual Meeting, "Development of a shelf life prediction model using Bayesian parameter estimation for kinetics of solid state gabapentin degradation", Washington DC, USA, Contributed. (2011).
22. Tinmanee, R., Stamatis, S., Dempah, E., Munson, E., Kirsch, L. E., AAPS Annual Meeting, "Modeling polymorphic transformations of gabapentin and assessing the effect of excipients using PXRD and ssNMR", Washington DC, USA, Contributed. (2011).
23. Chanvorachote, B., Qiu, J., Muangsiri, W., Nimmannit, U., Kirsch, L. E., AAPS Annual Meeting and Exposition, "The mechanism between PAMAM dendrimers and lipopeptide (daptomycin)", Washington DC, Contributed. (October 2011).
24. Tinmanee, R., Stamatis, S., Nguyen, Q., Zong, Z., Kirsch, L. E., NIPTE/FDA Research Symposium, "Formulation of a gabapentin drug degradation model that combines manufacturing and storage stress variables", Rockville, USA, Contributed. (June 2011).
25. Tinmanee, R., Zong, Z., Kirsch, L. E., NIPTE/FDA Research Symposium, "Role of excipients in the solid state lactamization of gabapentin", Rockville, USA, Contributed. (June 2011).
26. Qiu, J., Kirsch, L. E., AAPS National Biotechnology Conference, "The effects of aggregation and conformation on the ionization of lipopeptide (Daptomycin)", San Francisco, CA, Contributed. (May 2011).
27. Buckner, I., Dalal, N., Tinmanee, R., Zong, Z., Huang, H., Qiu, J., Kirsch, L. E., AAPS, "Excipient effects on the solid-state stability of gabapentin", New Orleans, Lousiana, USA, Contributed. (November 2010).
28. Qiu, J., Yu, L., Kirsch, L. E., AAPS Annual Meeting and Exposition, "Determination of the complex ionization behaviour of daptomycin", New Orleans, Louisiana, Contributed. (November 2010).
29. Zong, Z., Kirsch, L. E., Kaushal, A., Suryanarayanan, R., Dempah, E., Munson, E., FIP Pharmaceutical Sciences World Congress in Association with the AAPS Annual Meeting and Exposition, "A Kinetic Model for the Solid State Degradation of Gabapentin", New

Orleans, Louisiana, Contributed. (November 2010).

30. Kaushal, A., Dempah, E., Huang, H. G., Qiu, J., Munson, E., Kirsch, L. E., Suryanarayanan, R., FIP Pharmaceutical Sciences World Congress in Association with the AAPS Annual Meeting and Exposition, "Phase transformations in gabapentin during wet granulation and drying", New Orleans, Louisiana, Contributed. (November 2010).
31. Dempah, K., Kaushal, A., Huang, H. G., Suryanarayanan, R., Kirsch, L. E., Munson, E., FIP Pharmaceutical Sciences World Congress in Association with the AAPS Annual Meeting and Exposition, "Predicting Gabapentin Stability upon Processing using SSNMR", New Orleans, Louisiana, Contributed. (November 2010).
32. Kirsch, L. E., Department of Chemical and Biological Engineering, Illinois Institute of Technology, "On the Role of Physical Stability on the Chemical Instability of Pharmaceuticals", Chicago, IL, Invited. (October 21, 2010).
33. Kirsch, L. E., Primera Reunion Internacional De Ciencias Farmaceuticas (RICiFa 2010), "A Case Study on Linking Solid-state Stability to Manufacturing Design in the FDA's Quality-by-Design Pharmaceutical Development Paradigm", Cordoba, Argentina, Invited. (June 25, 2010).
34. Kaushal, A., Suryanarayanan, R., Zong, Z., Desai, S., Huang, H.-S., Khan, M., Kirsch, L. E., Barich, D. H., Munson, E. J., AAPS Annual Meeting, "Anhydrous and monohydrate gabapentin inter-conversion: Potential implications during solid dosage form manufacture", Los Angeles, Contributed. (2009).
35. Barich, D. H., Munson, E. J., Kaushal, A., Suryanarayanan, R., Zong, Z., Desai, S., Huang, H.-S., Khan, M., Kirsch, L. E., AAPS Annual Meeting, "Characterization of Gabapentin Forms and Stability using Solid-State NMR Spectroscopy", Los Angeles, Contributed. (2009).
36. Zong, Z., Desai, S., Kaushal, A., Barich, D., Huang, H., Munson, E., Suryanarayanan, R., Khan, M., Kirsch, L. E., AAPS Annual Meeting, "The Stabilizing Effect of Moisture on the Solid-State Degradation of Gabapentin", Los Angeles, Contributed. (2009).
37. Zong, Z., Desai, S., Huang, H.-S., Kirsch, L. E., Kaushal, A., Suryanarayanan, R., Barich, D. H., Munson, E. J., Wildfong, P., Buckner, I., Drennen, J., Pingali, K. C., Muzzio, F. J., Kayrak-Talay, D., Litster, J. D., Reklaitis, G., Bogner, R., Khan, M., AIChE Annual Meeting, "The Development of Methods to Link Design Space Models to Product Stability", Nashville, Contributed. (2009).
38. Kirsch, L. E., Symposium presentation at the University of Wisconsin, "Pharmaceutical Chemistry of a Lipopeptide Antibiotic (Daptomycin)", Invited. (March 27, 2009).
39. Qiu, J., Kirsch, L. E., AAPS Annual meeting, "The effects of aggregation on the pharmaceutical chemistry of daptomycin", Atlanta, Contributed. (November 2008).
40. Kirsch, L. E., NIPTE Stakeholders Meeting, "An Introduction to the NIPTE Curriculum", Chicago, Contributed. (April 2008).
41. Kirsch, L. E., Annual AAPS meeting, "Transforming Pharmaceutical Technology Education", San Diego, Invited. (2007).
42. Qiu, J., Kirsch, L. E., AAPS Annual Meeting, "Evaluation of Lipopeptide Aggregation Using Light Scattering, Fluorescence and NMR Spectroscopy", San Diego, Contributed. (November 2007).
43. Desai, S., Kirsch, L. E., AAPS Annual Meeting, "Ortho Substitution Effects in the Hydrolysis of Formanilides", San Diego, Contributed. (November 2007).
44. Naik, H., Kirsch, L. E., Fleckenstein, L., AAPS Annual Meeting, "Population pharmacokinetics of artesunate and its metabolite, dihydroartemisinin", San Diego, Contributed. (November 2007).

45. Chanvorachote, B., Kirsch, L. E., AAPS Annual Meeting, "Studies on the Binding between Daptomycin and PAMAM Dendrimers", San Diego, Contributed. (November 2007).
46. Zong, Z., Kirsch, L. E., AAPS Annual Meeting, "Studies on the Instability of Chlorhexidine", San Diego, Contributed. (November 2007).
47. Kirsch, L. E., AAPS Annual Meeting, "Transforming Pharmaceutical Technology Education: A NIPTE Proposal", Contributed. (November 2007).
48. Kirsch, L. E., Annual PDA Meeting, "NIPTE Roadmap", Las Vegas. (March 2007).
49. Kirsch, L. E., Science and Education Advisory Committee meeting, "NIPTE Roadmap", Chicago, Contributed. (March 2007).
50. Kirsch, L. E., Chemical and Biochemical Engineering Symposium Series, "Physical and Pharmaceutical Chemistry of Daptomycin", The University of Iowa, Invited. (February 15, 2007).
51. Zong, Z., Kirsch, L. E., AAPS meeting, "Kinetic Studies of the Formation of p-Chloroaniline from the Degradation of Chlorhexidine", Nashville, Contributed. (November 2005).
52. Gokhale, M., Kirsch, L. E., AAPS meeting, "Kinetics and Mechanisms of the Glycosylation of Weakly Basic Aromatic Amines and Monosaccharides", Nashville, Contributed. (November 2005).
53. Desai, S., Kirsch, L. E., AAPS meeting, "Preliminary Studies of Ortho Substitution Effects on Amide Hydrolysis using Formanilides as Model Compounds", Nashville, Contributed. (November 2005).
54. Kirsch, L. E., Pharmaceutical Forum, "Depot Injection Systems: Current Uses and Issues", London, England, Invited. (November 2005).
55. Kirsch, L. E., North Carolina Discussion Group, Research Triangle Part, "Adventures in Peptide Degradation Kinetics", Durham, NC, Invited. (June 6, 2005).
56. Gokhale, M., Kirsch, L. E., AAPS Annual Meeting, "The Effects of pH and Buffers on the Kinetics of Kynurenine Glycosylation", Baltimore, MD, Contributed. (November 2004).
57. Kirsch, L. E., Pharmaceutical Microbiology Forum, "Package Integrity Quality Assurance", Fairport, NY, Invited. (October 2004).
58. Gokhale, M., Kirsch, L. E., AAPS Annual Meeting, "Preliminary Kinetic Studies on the Reaction of Kynurenine with D-glucose", Stalt Lake City, Contributed. (October 2003).
59. Kirsch, L. E., University of North Carolina, College of Pharmacy, "Chemical Degradation of Pharmaceutical Peptide", Invited. (April 15, 2003).
60. Kirsch, L. E., Genentech, "The Science Behind Pharmaceutical Packaging Quality Assurance", South San Francisco, CA, Invited. (February 2003).
61. Muangsiri, W., Kirsch, L. E., Annual Meeting of the American Association of Pharmaceutical Scientists, "In Vitro Characterization of Macromolecular Antibiotic Prodrugs", Toronto, Canada, Contributed. (November 2002).
62. Muangsiri, W., Kirsch, L. E., Annual Meeting of the American Association of Pharmaceutical Scientists, "Preparation of Macromolecular Antibiotic Prodrugs", Toronto, Canada, Contributed. (November 2002).
63. Kirsch, L. E., Annual Meeting of the American Association of Pharmaceutical Scientists, "Techniques for Establishing Critical Leakage Specifications", Toronto, Canada, Contributed. (November 13, 2002).
64. Kalvakota, B., Kirsch, L. E., Redmon, M., Thakur, A., Annual Meeting of the American Association of Pharmaceutical Scientists, "The Degradation of (R,R)-formoterol-L-tartrate in Aqueous Solutions", Denver, Colorado, Contributed. (October 2001).
65. Joshi, A., Kirsch, L. E., Annual Meeting of the American Association of Pharmaceutical

Scientists, "The Relative Rates of Asparaginyl and Glutaminyl Deamidation in Glucagon Fragment 22-29 under Acidic Conditions", Denver, Colorado, Contributed. (October 2001).

66. Kirsch, L. E., Pulmonary Delivery and Disposition of Inhaled Aerosols Workshop, Controlled Release Society 28th International Symposium, "Protein and Peptide Stability in the Liquid and Solid States", San Diego, California, Contributed. (June 24, 2001).
67. Joshi, A., Kirsch, L. E., Annual Meeting of the Pharmaceutical Congress of the Americas, "Determination of Relative Cleavage and Deamidation Rates in Acidic Glucagon Solutions to Evaluate Sequence Effects", Orlando, Florida, Contributed. (March 2001).
68. Kirsch, L. E., Pharmacia, "Package Integrity Testing for Sterility Assurance", Portage, MI, Invited. (October 2000).
69. Kirsch, L. E., Cubist Pharmaceutical, "The Role of Aggregation in the Kinetics of Daptomycin Degradation", Cambridge, MA, Invited. (August 2000).
70. Joshi, A. B., Kirsch, L. E., 1999 Annual American Association of Pharmaceutical Scientists Meeting, "Acidic Degradation Pathways of Glucagon", New Orleans, Contributed. (November 1999).
71. Muangsiri, W., Kirsch, L. E., 1999 Annual American Association of Pharmaceutical Scientists Meeting, "Aqueous Degradation of Daptomycin in Alkaline Solutions", New Orleans, Contributed. (November 1999).
72. Nguyen, L., Kirsch, L. E., Wiencek, J., 1999 Annual American Association of Pharmaceutical Scientists Meeting, "Effects of Shear Stress on the Structural and Mechanical Characteristics of Glucagon Gel Systems", New Orleans, Contributed. (November 1999).
73. Zhang, X., Kirsch, L. E., 1999 Annual American Association of Pharmaceutical Scientists Meeting, "Microviscosity of the Emulsion Determined by Fluorescence Polarization", New Orleans, Contributed. (November 1999).
74. Kirsch, L. E., Zhang, Z., Muangsiri, W., Luner, P., Wurster, D., Redmon, M., 1999 Annual American Association of Pharmaceutical Scientists Meeting, "RR-Formterol (L) Tartrate Development", New Orleans, Contributed. (November 1999).
75. Kirsch, L. E., Majuru, S., Oh, E., Joshi, A., Luner, P., Wurster, D., Redmon, M., 1999 Annual American Association of Pharmaceutical Scientists Meeting, "S-Oxybutynin Preformulation Studies", New Orleans, Contributed. (November 1999).
76. Zhang, X., Kirsch, L. E., 1999 Annual American Association of Pharmaceutical Scientists Meeting, "Study of the Mechanism of Thermally-stressed Parenteral Fat Emulsion", New Orleans, Contributed. (November 1999).
77. Kirsch, L. E., PDA and American Association of Pharmaceutical Scientists Chicagoland discussion groups, "Debunking Pharmaceutical Package Integrity Testing", Chicago, Invited. (September 1999).
78. Zhang, X., Kirsch, L. E., 1997 Annual American Association of Pharmaceutical Scientists Meeting, "Drug Effects on the Coalescence Rate of Thermally-stressed Emulsions", San Francisco, Contributed. (November 1998).
79. Nguyen, L. T., Kirsch, L. E., 1998 Annual American Association of Pharmaceutical Scientists Meeting, "Establishing the Microbial Barrier Properties of Pharmaceutical Packaging by Physical Leak Rate Measurements", San Francisco, Contributed. (November 1998).
80. Kirsch, L. E., Israel Chapter of the PDA, "Pharmaceutical Package Integrity", Herzelia, Israel, Invited. (October 28, 1998).
81. Kirsch, L. E., Medical College of Virginia, "Pharmaceutical Instability of Peptides", Invited.

(September 1998).

82. Kirsch, L. E., Morton Guazzo, D., PDA Training and Research Center, "Leakage and Parenteral Packaging Seal Integrity", Baltimore, MD, Invited. (July 1998).
83. Kirsch, L. E., the International Blow-Fill-Seal Operators Meeting, "Current and Future State of Pharmaceutical Package Integrity", Cambridge, MA, Invited. (April 30, 1998).
84. Kirsch, L. E., Nguyen, L. T., Morton Guazzo, D., Scheire, R., Muangsiri, W., Western PDA meeting, "Methods for the Development of Indirect Correlations between Physical Leak Rate Methods and Microbial Ingress into Parenteral Packaging", San Francisco, Contributed. (March 1998).
85. Kirsch, L. E., ESI-Lederle, "Current Issues in Pharmaceutical Container/Closure Integrity Technologies", Invited. (February 2, 1998).
86. Nguyen, L. T., Gerth, R., Kirsch, L. E., 1997 Annual American Association of Pharmaceutical Scientists Meeting, "A Model for Predicting Helium Leak Rates of Defective Sealed Vials and Its Application in the Validation of Helium Leak Rate Method for Pharmaceutical Container/Closure Systems", Boston, Contributed. (November 1997).
87. Zhang, X., Kirsch, L. E., 1997 Annual American Association of Pharmaceutical Scientists Meeting, "An Assessment of Techniques for Evaluating the Physical Stability of Parenteral Microemulsions", Boston, Contributed. (November 1997).
88. Nguyen, L. T., Gerth, R., Moeckly, C. S., Kirsch, L. E., 1997 Annual American Association of Pharmaceutical Scientists Meeting, "Correlation of Mass Spectrometry-based Helium Leak Measurements to Microbial Ingress for Pharmaceutical Container/Closure Integrity Testing", Boston, Contributed. (November 1997).
89. Kirsch, L. E., Executive MBA program offered by the College of Business Administration at The University of Iowa, "A Technologist's View of the Pharmaceutical Industry", Invited. (August 1997).
90. Kirsch, L. E., Glaxo Welcome, "Pharmaceutical Container/Closure Integrity Technologies", Invited. (April 14, 1997).
91. Kirsch, L. E., PDA International Congress, "PDA Container/Closure Study", Osaka, Japan, Invited. (February 18, 1997).
92. Nguyen, L., Moeckly, C., Kirsch, L. E., 1996 Annual American Association of Pharmaceutical Scientists Meeting, "Pharmaceutical Container Closure Integrity by Mass Spectrometry-based Leak Detection", Seattle, Contributed. (1996).
93. Kirsch, L. E., 50th Annual PDA meeting, "Application of Mass Spectrometry Leak Testing to Pharmaceutical Package Integrity Quality Assurance", Philadelphia, Invited. (November 20, 1996).
94. Kirsch, L. E., Seminar at Fujisawa USA, "Pharmaceutical Container/Closure Integrity Technologies", Chicago, Invited. (April 19, 1996).
95. Sihn, Y., Guillory, K., Kirsch, L. E., 1995 Annual American Association of Pharmaceutical Scientists meeting, "Degradation Kinetics and Interaction Studies of Taurolidine Equilibrium Products with PVP in Aqueous Media", Contributed. (1995).
96. Kirsch, L. E., 1995 Annual American Association of Pharmaceutical Scientists Meeting, "Challenges in the Sterilization of Injectable Disperse Systems", Miami, Invited. (November 1995).
97. Kirsch, L. E., Genetics Institute, "Re-engineering Pharmaceutical Product Development", Andover, Invited. (December 1994).
98. Kirsch, L. E., Redmon, M. P., 16th Annual Midwest Biopharmaceutical Statistics Workshop, "Quality Tools Applied to Pharmaceutical Product Development: Quality Function Deployment, Business Function Deployment, and Failure Modes and Effects

Analysis", Invited. (May 1993).

99. Kirsch, L. E., Redmon, M. P., Arden House Conference, "Biopharmaceutical Product Development", Invited. (February 1993).
100. Kirsch, L. E., Annual American Association of Pharmaceutical Scientists Meeting, "New Method for Predicting Arrhenius Behavior in Accelerated Drug Degradation Studies", Washington DC, Contributed. (October 1991).
101. Kirsch, L. E., Virginia Commonwealth University, School of Pharmacy faculty and graduate students, "Degradation Kinetics Short Course and Simulation Laboratory", Invited. (April 1991).
102. Stout, P., Khoury, N., Mauger, J., Kirsch, L. E., Annual American Association of Pharmaceutical Scientists Meeting, "Human Zinc Insulin Suspension Release Kinetics", Las Vegas, Nevada, Contributed. (November 1990).
103. Kirsch, L. E., Land O Lakes meeting, "Protein Reactivity", Invited. (June 1990).
104. Kirsch, L. E., Lefeber, D., Riggin, R., Gearhart, D., Clone to Clinic Biotechnology Meeting, "The Susceptibility of Human Growth Hormone to In-process Degradation", Amsterdam, the Netherlands, Contributed. (March 1990).
105. Kirsch, L. E., University of Nebraska, College of Pharmacy, Pharmaceutical Sciences Research Retreat, "Strategies for Research Collaboration with Industrial Sites", Boystown, Nebraska, Invited. (November 1989).
106. Mauger, K., Shaeiwitz, J., Mauger, J., Kirsch, L. E., Annual American Association of Pharmaceutical Scientists meeting, "Mechanism of Crystalline Zinc Insulin Dissolution", Atlanta, Georgia, Contributed. (October 1989).
107. Kirsch, L. E., Annual American Association of Pharmaceutical Scientists meeting, "Protein Degradation Pathways in Parenteral Dosage Forms", Atlanta, Georgia, Invited. (October 1989).
108. Gearhart, D., Lefeber, D., Riggin, R., Kirsch, L. E., Annual American Association of Pharmaceutical Scientists meeting, "The Effects of Parenteral Sterilants on the Generation of Protein Degradation Products During Pharmaceutical Processing", Atlanta, Georgia, Contributed. (October 1989).
109. Khoury, N., Stout, P., Mauger, J., Shaeiwitz, J., Kirsch, L. E., ACS Colloid and Surface Science Symposium, "Dissolution of Recombinant Human Insulin Crystal", Seattle, Washington, Contributed. (June 1989).
110. Kirsch, L. E., Rho Chi lecturer, "Biotechnic Drug Development", Duquesne University, Invited. (December 1988).
111. Stout, P., Mauger, J., Koury, N., Kirsch, L. E., American Association of Pharmaceutical Scientists meeting, "Dissolution Characteristics of Changing Mixtures of Amorphous: Crystalline Humulin Zinc Insulin", Orlando, Florida, Contributed. (November 1988).
112. Gearhart, D., Kirsch, L. E., Annual American Association of Pharmaceutical Scientists meeting, "Dry-state Deamidation of Glucagon", Orlando, Florida, Contributed. (November 1988).
113. Kirsch, L. E., Short course presented to the West Virginia University, School of Pharmacy graduate students, "Degradation Kinetics Short Course and Simulation Laboratory", Invited. (May 1988).
114. Kirsch, L. E., West Virginia University, University of Kentucky, Duquesne University, Medical College of Virginia, Biochemical Development Seminar Series, "The Role of Transpeptidation and Deamidation in the Pharmaceutical Instability of Proteins and Peptides", Invited. (1987).
115. Kirsch, L. E., Biotechnology symposium at the American Association of Pharmaceutical

Scientists meeting, "The Role of Transpeptidation and Deamidation in the Pharmaceutical Instability of Proteins and Peptides", Boston, Invited. (June 1987).

116. Kirsch, L. E., Short Course presented to the West Virginia University, School of Pharmacy graduate students, "Degradation Kinetics Short Course and Simulation Laboratory", Invited. (May 1987).
117. Kirsch, L. E., Bucko, J., Smith, W., Akers, M., Hargrove, W., 1986 American Association of Pharmaceutical Scientists meeting, "Development of a Quantitative Model for the In Vitro and In Vivo Delivery Kinetics of CRIS, a Novel Intravenous System", Washington DC, Contributed. (November 1986).
118. Stout, P., Mauger, J., Kirsch, L. E., Khoury, N., Sheliga, T., Annual American Association of Pharmaceutical Scientists, "Dissolution of Lente Insulins", Washington DC, Contributed. (November 1986).
119. Kirsch, L. E., Humana Corporate Center, "IVAC CRIS System Performance", Louisville, Kentucky, Invited. (May 1986).
120. Kirsch, L. E., Delaware Valley Society of Hospital Pharmacists, "Drug Delivery with the IVAC CRIS System", Philadelphia, Pennsylvania, Invited. (April 1986).
121. Kirsch, L. E., Graduate Faculty Seminar, "Kinetics and Pharmacokinetics of Intravenous Drug Delivery", School of Pharmacy West Virginia, Invited. (January 1986).
122. Kirsch, L. E., American Society of Hospital Pharmacists 20th Midyear Clinical Meeting, "Drug Delivery with the IVAC CRIS System", New Orleans, Louisiana, Contributed. (December 1985).
123. Kirsch, L. E., Smith, W., Massey, E., Bechtel, L., Davies, D., Thirty-seventh National Meeting of the Academy of Pharmaceutical Sciences, "The Evaluation of Human Insulin Formulations by Kinetic Analysis of Time-Action Profiles in Rabbits", Philadelphia, Pennsylvania, Contributed. (October 1984).
124. Kirsch, L. E., Notari, R., 130th American Pharmaceutical Association Annual Meeting, "Kinetics and Mechanism of In Vitro Prodrug Conversion to Cytarabine (ARA-C)", New Orleans, Louisiana, Contributed. (April 1983).
125. Kirsch, L. E., Notari, R., 130th American Pharmaceutical Association Annual Meeting, "Pharmacokinetics of Prodrug Bioconversion to Cytarabine (ARC-C)", New Orleans, Louisiana, Contributed. (April 1983).

Grantsmanship

Over 55 research grants and contracts

PROFESSIONAL, GOVERNMENTAL, UNIVERSITY AND OTHER SERVICE

Professional/Clinical Services and Committees

Internal Committee

University of Iowa STEM Advisory Council. (2011 - 2013).
College of Pharmacy Curriculum Re-engineering Task Force, “Transformers”. (2009 - 2014).
Faculty Senate. (2008 - 2011).
College of Pharmacy IT Committee Chairman. (2008 - 2009).
Graduate College Council. (2006 - 2009).
College of Pharmacy Admissions Committee. (2007 - 2008).

College of Pharmacy Curriculum Committee. (2006 - 2007).
College of Pharmacy Continuing Education Oversight Committee. (2003 - 2006).
College of Pharmacy Industrial Consortium. (2003 - 2006).
College of Pharmacy Admissions Committee Chairman. (2001 - 2003).
College of Pharmacy Research Equipment Committee. (1999 - 2003).
Pharmaceutics Search Committee Chairman. (2001 - 2002).
Ad Hoc Planning Committee for the 1999 Collegiate Research Retreat. (1999).
Advisory Committee to the Vice President for Research for Medical and Biological Sciences. (1998 - 1999).

General

Member of the American Association of Pharmaceutical Scientists (1993 – present)
Member of USP <1207> Expert Panel. (January 2011 - 2013).
Editor-in-chief, AAPS Pharmaceutical Science and Technology Journal. (July 2008 – December, 2014).
Faculty Committee Leadership in the National Institute for Pharmaceutical Technology and Education, Faculty Committee, Chairman and Leadership Team (2009-2011): Education Roadmap, Co Chairman: Pharmaceutical Material Section of Technology Roadmap. (2005 - 2008). Chaired the education committee for NIPTE working on the design of a national curriculum in pharmaceutical technology. (2005 – 2008)
Editorial Advisory Board, Drug Development and Industrial Pharmacy. (June 2000 - 2009).
Member of the Parenteral Drug Association Executive Committee. (2000 - 2002).
Member of USP <1059> Advisory Committee of Excipient Quality. (January 2009 - January 2011).
PQRI Working Group Member, Aseptic Processing. (2003 - 2008).
Regulatory Affairs Advisory Board for the Parenteral Drug Association. (2003 - 2008).
Scientific Advisory Board for the Parenteral Drug Association. (2003 - 2008).
Strategic Planning Committee for the Parenteral Drug Association. (2003 - 2008).
Editorial Advisory Board, Pharmaceutical Development and Technology. (1995 - 2008).
Editor, The PDA Journal of Pharmaceutical Science and Technology. (February 2000 - June 2008).
Reviewer for United Arab Emirate University Research Fund. (2004).
The University of Iowa Research Review Committee in the Biological Sciences. (2003 - 2004).
Reviewer for State of Indiana 21st Century Fund proposals. (2003).
Member of the Ad Hoc National Institutes of Health SBIR and STTR Study Section for Drug Development and Delivery. (2000).
Reviewer for the National Science Foundation Directorate for Engineering. (2000).
Member of the Pharmaceutical Sciences Alliance Council, Aseptic Processing Advisory Panel, PDA-TRI Container/Closure Applied Research Task Force, and Faculty member for the Parenteral Drug Association Research and Training Center. (1998 - 1999).
Chairman of the American Association of Pharmaceutical Scientists Sterile Products Focus Group. (1997).
AAPS Pharmaceutical Technology Section Leadership Team. (1995 - 1997).
Conference co-chairman (with Dr. John Clements of the Royal Pharmaceutical Society of Great Britain) for the 1996 Arden House Conferences. (1996).

EXHIBIT B

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TYGACIL safely and effectively. See full prescribing information for TYGACIL.
TYGACIL® (tigecycline) FOR INJECTION for intravenous use
Initial U.S. Approval: 2005

WARNING: ALL-CAUSE MORTALITY

See full prescribing information for complete boxed warning.

All-cause mortality was higher in patients treated with TYGACIL than comparators in a meta-analysis of clinical trials. The cause of this mortality risk difference of 0.6% (95% CI 0.1, 1.2) has not been established. TYGACIL should be reserved for use in situations when alternative treatments are not suitable *[see Indications and Usage (1.4), Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

INDICATIONS AND USAGE

TYGACIL is a tetracycline-class antibacterial drug indicated in patients 18 years of age and older for:

- Complicated skin and skin structure infections (1.1)
- Complicated intra-abdominal infections (1.2)
- Community-acquired bacterial pneumonia (1.3)

Limitations of Use: TYGACIL is not indicated for treatment of diabetic foot infection or hospital-acquired pneumonia, including ventilator-associated pneumonia (1.4).

DOSAGE AND ADMINISTRATION

- Initial dose of 100 mg, followed by 50 mg every 12 hours administered intravenously over approximately 30 to 60 minutes. (2.1)
- Severe hepatic impairment (Child Pugh C): Initial dose of 100 mg followed by 25 mg every 12 hours. (2.2)

DOSAGE FORMS AND STRENGTHS

50 mg lyophilized powder for reconstitution in a single-dose 5 mL vial or 10 mL vial. (3)

CONTRAINDICATIONS

- Known hypersensitivity to tigecycline. (4)

WARNINGS AND PRECAUTIONS

- A meta-analysis of Phase 3 and 4 clinical trials demonstrated an increase in all-cause mortality in TYGACIL-treated patients compared to controls with a risk difference of 0.6% (95% CI 0.1, 1.2). The cause of this increase has not been established. An increase was also seen in a meta-analysis limited to the approved indications [0.6% (95% CI 0.0, 1.2)]. The greatest difference in mortality was seen in TYGACIL-treated patients with ventilator-associated pneumonia (5.1, 5.2).
- Anaphylaxis/anaphylactoid reactions have been reported with TYGACIL, and may be life-threatening. Exercise caution in patients with known hypersensitivity to tetracyclines. (5.3)
- Hepatic dysfunction and liver failure have been reported with TYGACIL. (5.4)
- Pancreatitis, including fatalities, has been reported with TYGACIL. If pancreatitis is suspected, then consider stopping TYGACIL. (5.5)
- TYGACIL may cause fetal harm when administered to a pregnant woman. (5.6)
- The use of TYGACIL during tooth development may cause permanent discoloration of the teeth. (5.7)
- *Clostridium difficile* associated diarrhea: evaluate if diarrhea occurs. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (incidence >5%) are nausea, vomiting, diarrhea, abdominal pain, headache, and increased SGPT. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Suitable anticoagulation test should be monitored if TYGACIL is administered to patients receiving warfarin. (7.1)

USE IN SPECIFIC POPULATIONS

- Pediatrics: Use in patients under 18 years of age is not recommended. Pediatric trials were not conducted because of the higher risk of mortality seen in adult trials (8.4)

See 17 for PATIENT COUNSELING INFORMATION.
Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ALL-CAUSE MORTALITY

An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in TYGACIL-treated patients versus comparator. The cause of this mortality risk difference of 0.6% (95% CI 0.1, 1.2) has not been established. TYGACIL should be reserved for use in situations when alternative treatments are not suitable *[see Indications and Usage (1.4), Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

TYGACIL is a tetracycline-class antibacterial drug indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the conditions listed below for patients 18 years of age and older:

1.1 Complicated Skin and Skin Structure Infections

Complicated skin and skin structure infections caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Streptococcus pyogenes, Enterobacter cloacae, Klebsiella pneumoniae,* and *Bacteroides fragilis.*

1.2 Complicated Intra-abdominal Infections

Complicated intra-abdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens,* and *Peptostreptococcus micros.*

1.3 Community-Acquired Bacterial Pneumonia

Community-acquired bacterial pneumonia caused by Streptococcus pneumoniae (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*.

1.4 Limitations of Use

TYGACIL is not indicated for the treatment of diabetic foot infections. A clinical trial failed to demonstrate non-inferiority of TYGACIL for treatment of diabetic foot infections.

TYGACIL is not indicated for the treatment of hospital-acquired or ventilator-associated pneumonia. In a comparative clinical trial, greater mortality and decreased efficacy were reported in TYGACIL-treated patients *[see Warnings and Precautions (5.2)]*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYGACIL and other antibacterial drugs, TYGACIL should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to tigecycline. TYGACIL may be initiated as empiric monotherapy before results of these tests are known.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosage and Administration

The recommended dosage regimen for TYGACIL is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous infusions of TYGACIL should be administered over approximately 30 to 60 minutes every 12 hours.

The recommended duration of treatment with TYGACIL for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The recommended duration of treatment with TYGACIL for community-acquired bacterial pneumonia is 7 to 14 days. The duration of

therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

2.2 Patients With Hepatic Impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of TYGACIL should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response *[see Clinical Pharmacology (12.3) and Use in Specific Populations (8.6)]*.

2.3 Pediatric Patients

The safety and efficacy of the proposed pediatric dosing regimens have not been evaluated due to the observed increase in mortality associated with tigecycline in adult patients. Tigecycline should not be used in pediatric patients unless no alternative antibacterial drugs are available. Under these circumstances, the following doses are suggested:

- Pediatric patients aged 8 to 11 years should receive 1.2 mg/kg of tigecycline every 12 hours intravenously to a maximum dose of 50 mg of tigecycline every 12 hours.
- Pediatric patients aged 12 to 17 years should receive 50 mg of tigecycline every 12 hours,

The proposed pediatric doses of tigecycline were chosen based on exposures observed in pharmacokinetic trials, which included small numbers of pediatric patients *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*.

2.4 Preparation and Handling

Each vial of TYGACIL should be reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, or Lactated Ringer's Injection, USP to achieve a concentration of 10 mg/mL of tigecycline. (Note: Each vial contains a 6% overage. Thus, 5 mL of reconstituted solution is equivalent to 50 mg of the drug.) The vial should be gently swirled until the drug dissolves. Withdraw 5 mL of the reconstituted solution from the vial and add to a 100 mL intravenous bag for infusion (for a 100 mg dose, reconstitute two vials; for a 50 mg dose, reconstitute one vial). The maximum concentration in the intravenous bag should be 1 mg/mL. The reconstituted solution should be yellow to orange in color; if not, the solution should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration (e.g., green or black) prior to administration. Once reconstituted, TYGACIL may be stored at room temperature (not to exceed 25°C/77°F) for up to 24 hours (up to 6 hours in the vial and the remaining time in the intravenous bag). If the storage conditions exceed 25°C (77°F) after reconstitution, tigecycline should be used immediately. Alternatively, TYGACIL mixed with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP may be stored refrigerated at 2° to 8°C (36° to 46°F) for up to 48 hours following immediate transfer of the reconstituted solution into the intravenous bag.

TYGACIL may be administered intravenously through a dedicated line or through a Y-site. If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of TYGACIL with 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP or Lactated Ringer's Injection, USP. Injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line.

Compatibilities

Compatible intravenous solutions include 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, and Lactated Ringer's Injection, USP. When administered through a Y-site, TYGACIL is

compatible with the following drugs or diluents when used with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP: amikacin, dobutamine, dopamine HCl, gentamicin, haloperidol, Lactated Ringer's, lidocaine HCl, metoclopramide, morphine, norepinephrine, piperacillin/tazobactam (EDTA formulation), potassium chloride, propofol, ranitidine HCl, theophylline, and tobramycin.

Incompatibilities

The following drugs should not be administered simultaneously through the same Y-site as TYGACIL: amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole and omeprazole.

3 DOSAGE FORMS AND STRENGTHS

Each single-dose 5 mL glass vial and 10 mL glass vial contain 50 mg of tigecycline as an orange lyophilized powder for reconstitution.

4 CONTRAINDICATIONS

TYGACIL is contraindicated for use in patients who have known hypersensitivity to tigecycline.

5 WARNINGS AND PRECAUTIONS

5.1 All-Cause Mortality

An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in TYGACIL-treated patients versus comparator-treated patients. In all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving TYGACIL and 3.0% (110/3646) of patients receiving comparator drugs. In a pooled analysis of these trials, based on a random effects model by trial weight, the adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between TYGACIL and comparator-treated patients. An analysis of mortality in all trials conducted for approved indications (cSSSI, cIAI, and CABP), including post-market trials showed an adjusted mortality rate of 2.5% (66/2640) for tigecycline and 1.8% (48/2628) for comparator, respectively. The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2).

The cause of this mortality difference has not been established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities. TYGACIL should be reserved for use in situations when alternative treatments are not suitable *[see Indications and Usage (1.4), Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

5.2 Mortality Imbalance and Lower Cure Rates in Hospital-Acquired Pneumonia

A trial of patients with hospital acquired, including ventilator-associated, pneumonia failed to demonstrate the efficacy of TYGACIL. In this trial, patients were randomized to receive TYGACIL (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received TYGACIL had lower cure rates (47.9% versus 70.1% for the clinically evaluable population).

In this trial, greater mortality was seen in patients with ventilator-associated pneumonia who received TYGACIL (25/131 [19.1%] versus 15/122 [12.3%] in comparator-treated patients) *[see Adverse Reactions (6.1)]*. Particularly high mortality was seen among TYGACIL-treated patients with ventilator-

associated pneumonia and bacteremia at baseline (9/18 [50.0%] versus 1/13 [7.7%] in comparator-treated patients).

5.3 Anaphylaxis/Anaphylactoid Reactions

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including TYGACIL, and may be life-threatening. TYGACIL is structurally similar to tetracycline-class antibiotics and should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics.

5.4 Hepatic Effects

Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.

5.5 Pancreatitis

Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. The diagnosis of acute pancreatitis should be considered in patients taking tigecycline who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. Cases have been reported in patients without known risk factors for pancreatitis. Patients usually improve after tigecycline discontinuation. Consideration should be given to the cessation of the treatment with tigecycline in cases suspected of having developed pancreatitis *[see Adverse Reactions (6.2)]*.

5.6 Use During Pregnancy

TYGACIL may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline *[see Use in Specific Populations (8.1)]*.

5.7 Tooth Development

The use of TYGACIL during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Results of studies in rats with TYGACIL have shown bone discoloration. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

5.8 *Clostridium difficile* Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.9 Patients With Intestinal Perforation

Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In cIAI studies (n=1642), 6 patients treated with TYGACIL and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with TYGACIL had higher APACHE II scores (median = 13) versus the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.

5.10 Tetracycline-Class Effects

TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL *[see Warnings and Precautions (5.5)]*.

5.11 Superinfection

As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

5.12 Development of Drug-Resistant Bacteria

Prescribing TYGACIL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 2514 patients were treated with TYGACIL. TYGACIL was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. Table 1 shows the incidence of treatment-emergent adverse reactions through test of cure reported in ≥2% of patients in these trials.

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in ≥ 2% of Patients Treated in Clinical Studies

Body System Adverse Reactions	TYGACIL (N=2514)	Comparators* (N=2307)
Body as a Whole		
Abdominal pain	6	4
Abscess	2	2
Asthenia	3	2
Headache	6	7
Infection	7	5
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	5	6
Metabolic and Nutritional		
Alkaline Phosphatase Increased	3	3
Amylase Increased	3	2
Bilirubinemia	2	1
BUN Increased	3	1
Healing Abnormal	3	2
Hyponatremia	2	1
Hypoproteinemia	5	3
SGOT Increased†	4	5
SGPT Increased†	5	5
Respiratory System		
Pneumonia	2	2
Nervous System		
Dizziness	3	3
Skin and Appendages		
Rash	3	4

* Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid.

† LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

In all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving TYGACIL and 3.0% (110/3646) of patients receiving comparator drugs. In a pooled analysis of these trials, based on a random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between TYGACIL and comparator-treated patients (see Table 2).

The cause of the imbalance has not been established. Generally, deaths were the result of worsening infection, complications of infection or underlying co-morbidities.

Table 2. Patients with Outcome of Death by Infection Type

	TYGACIL		Comparator		Risk Difference*
Infection Type	**n/N**	**%**	**n/N**	**%**	**% (95% CI)**
cSSSI	12/834	1.4	6/813	0.7	0.7 (-0.3, 1.7)
cIAI	42/1382	3.0	31/1393	2.2	0.8 (-0.4, 2.0)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.0, 2.4)
HAP	66/467	14.1	57/467	12.2	1.9 (-2.4, 6.3)
Non-VAP†	41/336	12.2	42/345	12.2	0.0 (-4.9, 4.9)
VAP†	25/131	19.1	15/122	12.3	6.8 (-2.1, 15.7)
RP	11/128	8.6	2/43	4.7	3.9 (-4.0, 11.9)
DFI	7/553	1.3	3/508	0.6	0.7 (-0.5, 1.8)
Overall Adjusted	150/3788	4.0	110/3646	3.0	0.6 (0.1, 1.2)‡

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI = Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP = Ventilator-associated pneumonia; RP = Resistant pathogens; DFI = Diabetic foot infections.
Note: The studies include 300, 305, 900 (cSSSI), 301, 306, 315, 316, 400 (cIAI), 308 and 313 (CAP), 311 (HAP), 307 [Resistant gram-positive pathogen study in patients with MRSA or Vancomycin-Resistant Enterococcus (VRE)], and 319 (DFI with and without osteomyelitis).

* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups. The 95% CI for each infection type was calculated using the normal approximation method without continuity correction.

† These are subgroups of the HAP population.

‡ Overall adjusted (random effects model by trial weight) risk difference estimate and 95% CI.

An analysis of mortality in all trials conducted for approved indications - cSSSI, cIAI, and CABP, including post-market trials (315, 400, 900) - showed an adjusted mortality rate of 2.5% (66/2640) for tigecycline and 1.8% (48/2628) for comparator, respectively. The adjusted risk difference for mortality stratified by trial weight was 0.6% (95% CI 0.0, 1.2).

In comparative clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with TYGACIL (7%) versus comparators (6%). Serious adverse events of sepsis/septic shock were more frequently reported for subjects treated with TYGACIL (2%) versus comparators (1%). Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established *[see Warnings and Precautions (5.9)]*.

The most common treatment-emergent adverse reactions were nausea and vomiting which generally occurred during the first 1 – 2 days of therapy. The majority of cases of nausea and vomiting associated with TYGACIL and comparators were either mild or moderate in severity. In patients treated with TYGACIL, nausea incidence was 26% (17% mild, 8% moderate, 1% severe) and vomiting incidence was 18% (11% mild, 6% moderate, 1% severe).

In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35% for TYGACIL and 9% for vancomycin/aztreonam; vomiting incidence was 20% for TYGACIL and 4% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25% for TYGACIL and 21% for imipenem/cilastatin; vomiting incidence was 20% for TYGACIL and 15% for imipenem/cilastatin. In patients treated for community-acquired bacterial pneumonia (CABP), nausea incidence was 24% for TYGACIL and 8% for levofloxacin; vomiting incidence was 16% for TYGACIL and 6% for levofloxacin.

Discontinuation from tigecycline was most frequently associated with nausea (1%) and vomiting (1%). For comparators, discontinuation was most frequently associated with nausea (<1%).

The following adverse reactions were reported infrequently (<2%) in patients receiving TYGACIL in clinical studies:

Body as a Whole: injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis

Cardiovascular System: thrombophlebitis

Digestive System: anorexia, jaundice, abnormal stools

Metabolic/Nutritional System: increased creatinine, hypocalcemia, hypoglycemia

Special Senses: taste perversion

Hemic and Lymphatic System: partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia

Skin and Appendages: pruritus

Urogenital System: vaginal moniliasis, vaginitis, leukorrhea

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of TYGACIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure.

- anaphylaxis/anaphylactoid reactions
- acute pancreatitis
- hepatic cholestasis, and jaundice
- severe skin reactions, including Stevens-Johnson Syndrome
- symptomatic hypoglycemia in patients with and without diabetes mellitus

7 DRUG INTERACTIONS

7.1 Warfarin

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin *[see Clinical Pharmacology (12.3)]*.

7.2 Oral Contraceptives

Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects—Pregnancy Category D *[see Warnings and Precautions (5.6)]*

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ^{14}C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was associated with reductions in fetal weights and an increased incidence of skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg·hr/mL and 6 mcg·hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

There are no adequate and well-controlled studies of tigecycline in pregnant women. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Results from animal studies using ^{14}C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman *[see Warnings and Precautions (5.7)]*.

8.4 Pediatric Use

Use in patients under 18 years of age is not recommended. Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of the increased mortality observed in tigecycline-treated adult patients in clinical trials, pediatric trials of tigecycline to evaluate the safety and efficacy of tigecycline were not conducted.

In situations where there are no other alternative antibacterial drugs, pediatric dosing has been proposed based on data from pediatric pharmacokinetic studies *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

Because of effects on tooth development, use in patients under 8 years of age is not recommended *[see Warnings and Precautions (5.7)]*.

8.5 Geriatric Use

Of the total number of subjects who received TYGACIL in Phase 3 clinical studies (n=2514), 664 were 65 and over, while 288 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

No significant difference in tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of tigecycline *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.2)]*.

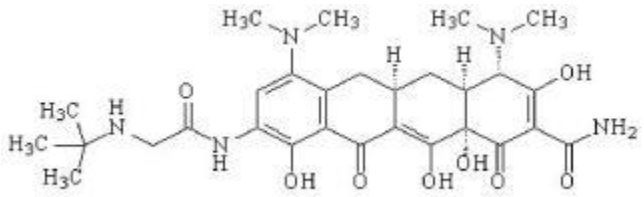
10 OVERDOSAGE

No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of TYGACIL at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose intravenous toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD_{50}) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD_{50} was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.

11 DESCRIPTION

TYGACIL (tigecycline) is a tetracycline derivative (a glycylcycline) for intravenous infusion. The chemical name of tigecycline is (4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-butylamino)acetamido]-4,7-bis (dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide. The empirical formula is $C_{29}H_{39}N_5O_8$ and the molecular weight is 585.65.

The following represents the chemical structure of tigecycline:



TYGACIL is an orange lyophilized powder or cake. Each TYGACIL vial contains 50 mg tigecycline lyophilized powder for reconstitution for intravenous infusion and 100 mg of lactose monohydrate. The pH is adjusted with hydrochloric acid, and if necessary sodium hydroxide. The product does not contain preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tigecycline is an antibacterial drug *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

No significant effect of a single intravenous dose of TYGACIL 50 mg or 200 mg on QTc interval was detected in a randomized, placebo- and active-controlled four-arm crossover thorough QTc study of 46 healthy subjects.

12.3 Pharmacokinetics

The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses based on pooled data from clinical pharmacology studies are summarized in Table 3. Intravenous infusions of tigecycline were administered over approximately 30 to 60 minutes.

Table 3. Mean (CV%) Pharmacokinetic Parameters of Tigecycline

	Single Dose 100 mg (N=224)	Multiple Dose* 50 mg every 12h (N=103)
C_{max} (mcg/mL)†	1.45 (22%)	0.87 (27%)
C_{max} (mcg/mL)‡	0.90 (30%)	0.63 (15%)
AUC (mcg·h/mL)	5.19 (36%)	- -
$AUC_{0–24h}$ (mcg·h/mL)	- -	4.70 (36%)
C_{min} (mcg/mL)	- -	0.13 (59%)
$t_{½}$ (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CL_r (mL/min)	38.0 (82%)	51.0 (58%)
V_{ss} (L)	568 (43%)	639 (48%)

* 100 mg initially, followed by 50 mg every 12 hours
† 30-minute infusion
‡ 60-minute infusion

Distribution

The *in vitro* plasma protein binding of tigecycline ranges from approximately 71% to 89% at concentrations observed in clinical studies (0.1 to 1.0 mcg/mL). The steady-state volume of distribution of tigecycline averaged 500 to 700 L (7 to 9 L/kg), indicating tigecycline is extensively distributed beyond the plasma volume and into the tissues.

Following the administration of tigecycline 100 mg followed by 50 mg every 12 hours to 33 healthy volunteers, the tigecycline $AUC_{0–12h}$ (134 mcg·h/mL) in alveolar cells was approximately 78-fold higher than the $AUC_{0–12h}$ in the serum, and the $AUC_{0–12h}$ (2.28 mcg·h/mL) in epithelial lining fluid was approximately 32% higher than the $AUC_{0–12h}$ in serum. The $AUC_{0–12h}$ (1.61 mcg·h/mL) of tigecycline in skin blister fluid was approximately 26% lower than the $AUC_{0–12h}$ in the serum of 10 healthy subjects.

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Concentrations at 4 hours after tigecycline administration were higher in gallbladder (38-fold, n=6), lung (3.7-fold, n=5), and colon (2.3-fold, n=6),

and lower in synovial fluid (0.58-fold, n=5), and bone (0.35-fold, n=6) relative to serum. The concentration of tigecycline in these tissues after multiple doses has not been studied.

Metabolism

Tigecycline is not extensively metabolized. *In vitro* studies with tigecycline using human liver microsomes, liver slices, and hepatocytes led to the formation of only trace amounts of metabolites. In healthy male volunteers receiving ^{14}C-tigecycline, tigecycline was the primary ^{14}C-labeled material recovered in urine and feces, but a glucuronide, an N-acetyl metabolite, and a tigecycline epimer (each at no more than 10% of the administered dose) were also present.

Elimination

The recovery of total radioactivity in feces and urine following administration of ^{14}C-tigecycline indicates that 59% of the dose is eliminated by biliary/fecal excretion, and 33% is excreted in urine. Approximately 22% of the total dose is excreted as unchanged tigecycline in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

Specific Populations

Patients with Hepatic Impairment

In a study comparing 10 patients with mild hepatic impairment (Child Pugh A), 10 patients with moderate hepatic impairment (Child Pugh B), and 5 patients with severe hepatic impairment (Child Pugh C) to 23 age and weight matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25% and the half-life of tigecycline was prolonged by 23% in patients with moderate hepatic impairment (Child Pugh B). Systemic clearance of tigecycline was reduced by 55%, and the half-life of tigecycline was prolonged by 43% in patients with severe hepatic impairment (Child Pugh C). Dosage adjustment is necessary in patients with severe hepatic impairment (Child Pugh C) *[see Use in Specific Populations (8.6) and Dosage and Administration (2.2)]*.

Patients with Renal Impairment

A single dose study compared 6 subjects with severe renal impairment (creatinine clearance <30 mL/min), 4 end stage renal disease (ESRD) patients receiving tigecycline 2 hours before hemodialysis, 4 ESRD patients receiving tigecycline 1 hour after hemodialysis, and 6 healthy control subjects. The pharmacokinetic profile of tigecycline was not significantly altered in any of the renally impaired patient groups, nor was tigecycline removed by hemodialysis. No dosage adjustment of TYGACIL is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Geriatric Patients

No significant differences in pharmacokinetics were observed between healthy elderly subjects (n=15, age 65–75; n=13, age >75) and younger subjects (n=18) receiving a single 100-mg dose of TYGACIL. Therefore, no dosage adjustment is necessary based on age *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

A single-dose safety, tolerability, and pharmacokinetic study of tigecycline in pediatric patients aged 8 –16 years who recently recovered from infections was conducted. The doses administered were 0.5, 1, or 2 mg/kg. The study showed that for children aged 12–16 years (n = 16) a dosage of 50 mg twice daily would likely result in exposures comparable to those observed in adults with the approved dosing regimen. Large variability observed in children aged 8 to 11 years of age (n = 8) required additional study to determine the appropriate dosage.

A subsequent tigecycline dose-finding study was conducted in 8–11 year old patients with cIAI, cSSSI, or CABP. The doses of tigecycline studied were 0.75 mg/kg (n = 17), 1 mg/kg (n = 21), and 1.25 mg/kg (n=20). This study showed that for children aged 8–11 years, a 1.2 mg/kg dose would likely result in exposures comparable to those observed in adults resulting with the approved dosing regimen *[see Dosage and Administration (2.3)]*.

Gender

In a pooled analysis of 38 women and 298 men participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance between women (20.7±6.5 L/h) and men (22.8±8.7 L/h). Therefore, no dosage adjustment is necessary based on gender.

Race

In a pooled analysis of 73 Asian subjects, 53 Black subjects, 15 Hispanic subjects, 190 White subjects, and 3 subjects classified as "other" participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance among the Asian subjects (28.8±8.8 L/h), Black subjects (23.0±7.8 L/h), Hispanic subjects (24.3±6.5 L/h), White subjects (22.1±8.9 L/h), and "other" subjects (25.0±4.8 L/h). Therefore, no dosage adjustment is necessary based on race.

Drug Interactions

TYGACIL (100 mg followed by 50 mg every 12 hours) and digoxin (0.5 mg followed by 0.25 mg, orally, every 24 hours) were co-administered to healthy subjects in a drug interaction study. Tigecycline slightly decreased the C_{max} of digoxin by 13%, but did not affect the AUC or clearance of digoxin. This small change in C_{max} did not affect the steady-state pharmacodynamic effects of digoxin as measured by changes in ECG intervals. In addition, digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment of either drug is necessary when TYGACIL is administered with digoxin.

Concomitant administration of TYGACIL (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single-dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, an increase in C_{max} by 38% and 43% and an increase in AUC by 68% and 29%, respectively. Tigecycline did not significantly alter the effects of warfarin on INR. In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.

In vitro studies in human liver microsomes indicate that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome P450 (CYP) isoforms: 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. Therefore, TYGACIL is not expected to alter the metabolism of drugs metabolized by these enzymes. In addition, because tigecycline is not extensively metabolized, clearance of tigecycline is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.

12.4 Microbiology

Mechanism of Action

Tigecycline, a glycylcycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. Tigecycline carries a glycylamido moiety attached to the 9-position of minocycline. The substitution pattern is not present in any naturally occurring or semisynthetic tetracycline and imparts certain microbiologic properties to tigecycline. In general, tigecycline is considered bacteriostatic; however, TYGACIL has demonstrated bactericidal activity against isolates of *S. pneumoniae* and *L. pneumophila*.

Mechanism(s) of Resistance

To date there has been no cross-resistance observed between tigecycline and other antibacterials. Tigecycline is not affected by the two major tetracycline-resistance mechanisms, ribosomal protection and efflux. Additionally, tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target-site modifications, macrolide efflux pumps or enzyme target changes (e.g. gyrase/topoisomerases). Tigecycline resistance in some bacteria (e.g. *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex) is associated with multi-drug resistant (MDR) efflux pumps.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterials.

Tigecycline has been shown to be active against most of the following bacteria, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Facultative Gram-positive bacteria

Enterococcus faecalis (vancomycin-susceptible isolates)

Staphylococcus aureus (methicillin-susceptible and -resistant isolates)

Streptococcus agalactiae

Streptococcus anginosus grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*)

Streptococcus pneumoniae (penicillin-susceptible isolates)

Streptococcus pyogenes

Facultative Gram-negative bacteria

Citrobacter freundii

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae (beta-lactamase negative isolates)

Klebsiella oxytoca

Klebsiella pneumoniae

Legionella pneumophila

Anaerobic bacteria

Bacteroides fragilis

Bacteroides thetaiotaomicron

Bacteroides uniformis

Bacteroides vulgatus

Clostridium perfringens

Peptostreptococcus micros

At least 90% of the following bacteria exhibit *in vitro* minimum inhibitory concentrations (MICs) that are at concentrations that are achievable using the prescribed dosing regimens. However, the clinical

significance of this is unknown because the safety and effectiveness of tigecycline in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Facultative Gram-positive bacteria

Enterococcus avium

Enterococcus casseliflavus

Enterococcus faecalis (vancomycin-resistant isolates)

Enterococcus faecium (vancomycin-susceptible and -resistant isolates)

Enterococcus gallinarum

Listeria monocytogenes

Staphylococcus epidermidis (methicillin-susceptible and -resistant isolates)

Staphylococcus haemolyticus

Facultative Gram-negative bacteria

Acinetobacter baumannii[1]

Aeromonas hydrophila

Citrobacter koseri

Enterobacter aerogenes

Haemophilus influenzae (ampicillin-resistant)

Haemophilus parainfluenzae

Pasteurella multocida

Serratia marcescens

Stenotrophomonas maltophilia

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1 There have been reports of the development of tigecycline resistance in *Acinetobacter* infections seen during the course of standard treatment. Such resistance appears to be attributable to an MDR efflux pump mechanism. While monitoring for relapse of infection is important for all infected patients, more frequent monitoring in this case is suggested. If relapse is suspected, blood and other specimens should be obtained and cultured for the presence of bacteria. All bacterial isolates should be identified and tested for susceptibility to tigecycline and other appropriate antimicrobials.

Anaerobic bacteria

Bacteroides distasonis

Bacteroides ovatus

Peptostreptococcus spp.

Porphyromonas spp.

Prevotella spp.

Other bacteria

Mycobacterium abscessus

Mycobacterium fortuitum

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure based on dilution methods (broth, agar, or microdilution)[1,3,4] or equivalent using standardized inoculum and concentrations of tigecycline. For broth dilution tests for aerobic organisms, MICs must be determined in testing medium that is fresh (<12h old). The MIC values should be interpreted according to the criteria provided in Table 4.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The standardized procedure[2,4] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 mcg tigecycline to test the susceptibility of bacteria to tigecycline. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for tigecycline. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 mcg tigecycline disk should be interpreted according to the criteria in Table 4.

Anaerobic Techniques

Anaerobic susceptibility testing with tigecycline should be done by the agar dilution method[3] since quality control parameters for broth-dilution are not established.

Table 4. Susceptibility Test Result Interpretive Criteria for Tigecycline

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus (including methicillin-resistant isolates)	≤0.5*	-	-	≥19	-	-
Streptococcus spp. other than *S. pneumoniae*	≤0.25*	-	-	≥19	-	-
Streptococcus pneumoniae	≤0.06*	-	-	≥19	-	-
Enterococcus faecalis (vancomycin-susceptible isolates)	≤0.25*	-	-	≥19	-	-

* The current absence of resistant isolates precludes defining any results other than "Susceptible." Isolates yielding MIC results suggestive of "Nonsusceptible" category should be submitted to reference laboratory for further testing.

† Tigecycline has decreased *in vitro* activity against *Morganella* spp., *Proteus* spp. and *Providencia* spp.

‡ Agar dilution

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae†	≤2	4	≥8	≥19	15–18	≤14
Haemophilus influenzae	≤0.25*	-	-	≥19	-	-
Anaerobes‡	≤4	8	≥16	n/a	n/a	n/a

* The current absence of resistant isolates precludes defining any results other than "Susceptible." Isolates yielding MIC results suggestive of "Nonsusceptible" category should be submitted to reference laboratory for further testing.

† Tigecycline has decreased *in vitro* activity against *Morganella* spp., *Proteus* spp. and *Providencia* spp.

‡ Agar dilution

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures.[1,2,3,4] Standard tigecycline powder should provide the MIC values provided in Table 5. For the diffusion technique using the 15 mcg tigecycline disk the criteria provided in Table 5 should be achieved.

Table 5. Acceptable Quality Control Ranges for Susceptibility Testing

QC organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Staphylococcus aureus ATCC 25923	Not Applicable	20–25
Staphylococcus aureus ATCC 29213	0.03–0.25	Not Applicable
Escherichia coli ATCC 25922	0.03–0.25	20–27
Enterococcus faecalis ATCC 29212	0.03–0.12	Not Applicable

ATCC = American Type Culture Collection

* Agar dilution

QC organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Streptococcus pneumoniae ATCC 49619	0.016–0.12	23–29
Haemophilus influenzae ATCC 49247	0.06–0.5	23–31
Bacteroides fragilis[*] ATCC 25285	0.12–1	Not Applicable
Bacteroides thetaiotaomicron[*] ATCC 29741	0.5–2	Not Applicable
Eubacterium lentum[*] ATCC 43055	0.06–0.5	Not Applicable
Clostridium difficile[*] ATCC 70057	0.12–1	Not Applicable

ATCC = American Type Culture Collection

[*] Agar dilution

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of tigecycline. No mutagenic or clastogenic potential was found in a battery of tests, including *in vitro* chromosome aberration assay in Chinese hamster ovary (CHO) cells, *in vitro* forward mutation assay in CHO cells (HGRPT locus), *in vitro* forward mutation assays in mouse lymphoma cells, and *in vivo* mouse micronucleus assay. Tigecycline did not affect mating or fertility in rats at exposures up to 5 times the human daily dose based on AUC (28 mcg·hr/mL at 12 mg/kg/day). In female rats, there were no compound-related effects on ovaries or estrous cycles at exposures up to 5 times the human daily dose based on AUC.

13.2 Animal Toxicology and/or Pharmacology

In two week studies, decreased erythrocytes, reticulocytes, leukocytes, and platelets, in association with bone marrow hypocellularity, have been seen with tigecycline at exposures of 8 times and 10 times the human daily dose based on AUC in rats and dogs, (AUC of approximately 50 and 60 mcg·hr/mL at doses of 30 and 12 mg/kg/day) respectively. These alterations were shown to be reversible after two weeks of dosing.

14 CLINICAL STUDIES

14.1 Complicated Skin and Skin Structure Infections

TYGACIL was evaluated in adults for the treatment of complicated skin and skin structure infections (cSSSI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 300 and 305). These studies compared TYGACIL (100 mg intravenous initial dose followed by 50 mg every 12 hours) with vancomycin (1 g intravenous every 12 hours)/aztreonam (2 g intravenous every 12 hours) for 5 to 14 days. Patients with complicated deep soft tissue infections including wound infections and cellulitis (≥10 cm, requiring surgery/drainage or with complicated underlying disease), major

abscesses, infected ulcers, and burns were enrolled in the studies. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. See Table 6. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 7.

Table 6. Clinical Cure Rates from Two Studies in Complicated Skin and Skin Structure Infections after 5 to 14 Days of Therapy

	TYGACIL* n/N (%)	Vancomycin/Aztreonam† n/N (%)
Study 300		
CE	165/199 (82.9)	163/198 (82.3)
c-mITT	209/277 (75.5)	200/260 (76.9)
Study 305		
CE	200/223 (89.7)	201/213 (94.4)
c-mITT	220/261 (84.3)	225/259 (86.9)

* 100 mg initially, followed by 50 mg every 12 hours

† Vancomycin (1 g every 12 hours)/Aztreonam (2 g every 12 hours)

Table 7. Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Skin and Skin Structure Infections*

Pathogen	TYGACIL n/N (%)	Vancomycin/Aztreonam n/N (%)
Escherichia coli	29/36 (80.6)	26/30 (86.7)
Enterobacter cloacae	10/12 (83.3)	15/15 (100)
Enterococcus faecalis (vancomycin-susceptible only)	15/21 (71.4)	19/24 (79.2)
Klebsiella pneumoniae	12/14 (85.7)	15/16 (93.8)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	124/137 (90.5)	113/120 (94.2)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	79/95 (83.2)	46/57 (80.7)
Streptococcus agalactiae	8/8 (100)	11/14 (78.6)
Streptococcus anginosus grp.†	17/21 (81.0)	9/10 (90.0)
Streptococcus pyogenes	31/32 (96.9)	24/27 (88.9)
Bacteroides fragilis	7/9 (77.8)	4/5 (80.0)

* Two cSSSI pivotal studies and two Resistant Pathogen studies

† Includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*

14.2 Complicated Intra-abdominal Infections

TYGACIL was evaluated in adults for the treatment of complicated intra-abdominal infections (cIAI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 301 and 306). These studies compared TYGACIL (100 mg intravenous initial dose followed by 50 mg every 12 hours) with imipenem/cilastatin (500 mg intravenous every 6 hours) for 5 to 14 days. Patients with complicated diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis were enrolled in the studies. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the microbiologically evaluable (ME) and the microbiologic modified intent-to-treat (m-mITT) patients. See Table 8. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 9.

Table 8. Clinical Cure Rates from Two Studies in Complicated Intra-abdominal Infections after 5 to 14 Days of Therapy

	TYGACIL* n/N (%)	Imipenem/Cilastatin† n/N (%)
Study 301		
ME	199/247 (80.6)	210/255 (82.4)
m-mITT	227/309 (73.5)	244/312 (78.2)
Study 306		
ME	242/265 (91.3)	232/258 (89.9)
m-mITT	279/322 (86.6)	270/319 (84.6)

* 100 mg initially, followed by 50 mg every 12 hours

† Imipenem/Cilastatin (500 mg every 6 hours)

Table 9. Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Intra-abdominal Infections*

Pathogen	TYGACIL n/N (%)	Imipenem/Cilastatin n/N (%)
Citrobacter freundii	12/16 (75.0)	3/4 (75.0)
Enterobacter cloacae	15/17 (88.2)	16/17 (94.1)
Escherichia coli	284/336 (84.5)	297/342 (86.8)
Klebsiella oxytoca	19/20 (95.0)	17/19 (89.5)
Klebsiella pneumoniae	42/47 (89.4)	46/53 (86.8)
Enterococcus faecalis	29/38 (76.3)	35/47 (74.5)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	26/28 (92.9)	22/24 (91.7)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	16/18 (88.9)	1/3 (33.3)
Streptococcus anginosus grp.†	101/119 (84.9)	60/79 (75.9)
Bacteroides fragilis	68/88 (77.3)	59/73 (80.8)

* Two cIAI pivotal studies and two Resistant Pathogen studies

† Includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*

Pathogen	TYGACIL n/N (%)	Imipenem/Cilastatin n/N (%)
Bacteroides thetaiotaomicron	36/41 (87.8)	31/36 (86.1)
Bacteroides uniformis	12/17 (70.6)	14/16 (87.5)
Bacteroides vulgatus	14/16 (87.5)	4/6 (66.7)
Clostridium perfringens	18/19 (94.7)	20/22 (90.9)
Peptostreptococcus micros	13/17 (76.5)	8/11 (72.7)

* Two cIAI pivotal studies and two Resistant Pathogen studies

† Includes *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*

14.3 Community-Acquired Bacterial Pneumonia

TYGACIL was evaluated in adults for the treatment of community-acquired bacterial pneumonia (CABP) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 308 and 313). These studies compared TYGACIL (100 mg intravenous initial dose followed by 50 mg every 12 hours) with levofloxacin (500 mg intravenous every 12 or 24 hours). In one study (Study 308), after at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms. Total therapy was 7 to 14 days. Patients with community-acquired bacterial pneumonia who required hospitalization and intravenous therapy were enrolled in the studies. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the co-primary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (c-mITT) patients. See Table 10. Clinical cure rates at TOC by pathogen in the microbiologically evaluable patients are presented in Table 11.

Table 10. Clinical Cure Rates from Two Studies in Community-Acquired Bacterial Pneumonia after 7 to 14 Days of Total Therapy

	TYGACIL* n/N (%)	Levofloxacin† n/N (%)	95% CI‡
Study 308§			
CE	125/138 (90.6)	136/156 (87.2)	(-4.4, 11.2)
c-mITT	149/191 (78)	158/203 (77.8)	(-8.5, 8.9)
Study 313			
CE	128/144 (88.9)	116/136 (85.3)	(-5.0, 12.2)
c-mITT	170/203 (83.7)	163/200 (81.5)	(-5.6, 10.1)

* 100 mg initially, followed by 50 mg every 12 hours

† Levofloxacin (500 mg intravenous every 12 or 24 hours)

‡ 95% confidence interval for the treatment difference

§ After at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms in Study 308.

Table 11. Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Community-Acquired Bacterial Pneumonia*

Pathogen	TYGACIL n/N (%)	Levofloxacin n/N (%)
Haemophilus influenzae	14/17 (82.4)	13/16 (81.3)
Legionella pneumophila	10/10 (100.0)	6/6 (100.0)
Streptococcus pneumoniae (penicillin-susceptible only)†	44/46 (95.7)	39/44 (88.6)

* Two CABP studies

† Includes cases of concurrent bacteremia [cure rates of 20/22 (90.9%) versus 13/18 (72.2%) for TYGACIL and levofloxacin respectively]

To further evaluate the treatment effect of tigecycline, a post-hoc analysis was conducted in CABP patients with a higher risk of mortality, for whom the treatment effect of antibiotics is supported by historical evidence. The higher-risk group included CABP patients from the two studies with any of the following factors:

- Age ≥50 years
- PSI score ≥3
- *Streptococcus pneumoniae* bacteremia

The results of this analysis are shown in Table 12. Age ≥50 was the most common risk factor in the higher-risk group.

Table 12. Post-hoc Analysis of Clinical Cure Rates in Patients with Community-Acquired Bacterial Pneumonia Based on Risk of Mortality*

	TYGACIL n/N (%)	Levofloxacin n/N (%)	95% CI†
Study 308‡			
CE			
Higher risk			
Yes	93/103 (90.3)	84/102 (82.4)	(-2.3, 18.2)
No	32/35 (91.4)	52/54 (96.3)	(-20.8, 7.1)
c-mITT			
Higher risk			
Yes	111/142 (78.2)	100/134 (74.6)	(-6.9, 14)
No	38/49 (77.6)	58/69 (84.1)	(-22.8, 8.7)
Study 313			
CE			
Higher risk			
Yes	95/107 (88.8)	68/85 (80)	(-2.2, 20.3)
No	33/37 (89.2)	48/51 (94.1)	(-21.1, 8.6)
c-mITT			

* Patients at higher risk of death include patients with any one of the following: ≥50 year of age; PSI score ≥3; or bacteremia due to *Streptococcus pneumoniae*

† 95% confidence interval for the treatment difference

‡ After at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms in Study 308.

	TYGACIL n/N (%)	Levofloxacin n/N (%)	95% CI†
Higher risk			
Yes	112/134 (83.6)	93/120 (77.5)	(-4.2, 16.4)
No	58/69 (84.1)	70/80 (87.5)	(-16.2, 8.8)

* Patients at higher risk of death include patients with any one of the following: ≥50 year of age; PSI score ≥3; or bacteremia due to *Streptococcus pneumoniae*

† 95% confidence interval for the treatment difference

‡ After at least 3 days of intravenous therapy, a switch to oral levofloxacin (500 mg daily) was permitted for both treatment arms in Study 308.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Ninth Edition*. CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition.* CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
3. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard - Eight Edition*. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087 USA, 2012.
4. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third Informational Supplement*. CLSI document M100-S23. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.

16 HOW SUPPLIED/STORAGE AND HANDLING

TYGACIL (tigecycline) for injection is supplied in a single-dose 5 mL glass vial or 10 mL glass vial, each containing 50 mg tigecycline lyophilized powder for reconstitution.

Supplied:

5 mL - 10 vials/box. NDC 0008-4990-02

10 mL - 10 vials/box. NDC 0008-4990-20

Prior to reconstitution, TYGACIL should be stored at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.] Once reconstituted, TYGACIL may be stored at room temperature (not to exceed 25°C/77°F) for up to 24 hours (up to 6 hours in the vial and the remaining time in the intravenous bag). If the storage conditions exceed 25°C (77°F) after reconstitution, tigecycline should be used immediately. Alternatively, TYGACIL mixed with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP may be stored refrigerated at 2° to 8°C (36° to 46°F) for up to 48 hours following immediate transfer of the reconstituted solution into the intravenous bag. Reconstituted solution must be transferred and further diluted for intravenous infusion.

17 PATIENT COUNSELING INFORMATION

- Patients should be counseled that antibacterial drugs including TYGACIL should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When TYGACIL is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by TYGACIL or other antibacterial drugs in the future.
- Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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EXHIBIT C

What is pH

pH is a measure of the hydorgen ion concentration of a solution. Solutions with a high concentration of hydrogen ions have a low pH and solutions with a low concentrations of H+ ions have a high pH. This may seem like a confusion way to express these reationships, and it is, until you understand what pH stands for. The equation that defines pH is given as follows:

pH=-log[H+] concentration,

which is read:

the pH is equal to minus the log of the H+ concentration.

For example is the H+ concentration is very low, lets say about 0.0000001M, then the pH is

pH= -log[.0000001] whis is the same as -log[1 X 10-7]

the term log[1 X 10-7] = -7

- (-7) = 7

Look at the following table

hydrogen ion concetration	pH	solutions with a pH of
.1M	1	
.01M	2	coke and orange juice
.001	3	
.0001	4	
.00001	5	black coffee
.000001	6	
.0000001	7	pure water
.00000001	8	
.000000001	9	baking soda
.0000000001	10	
.00000000001	11	
.000000000001	12	household bleach
.0000000000001	13	oven cleaner

From this table you will notice a few relationships

- a difference of one pH unit (ie from pH 2 to pH 3) is a ten fold (10X) difference in H+ ion concentration.

- pure water should have a pH of 7.0
- solutions with a pH below 7.0 are termed acidic and solutions with a pH above 7.0 are termed basic.

EXHIBIT D

Yokogawa and Hamilton™ in the Biotech and Pharmaceutical Industry

Working Together To Bring You Best-In-Class Analytical Solutions

BU 12A0A2-E0A2-E-A

Hamilton™ pH Sensors

Hamilton's™ series of combination pH sensors have been specifically designed to meet the sever requirements of the pharmaceutical and biotech industries.

These sensors feature the most recent technological advancements in reference systems, reference electrolytes, reference junctions, and formulations of pH glass.

These advancements ensure excellent long-term stability and accuracy, after the repeated sterilization typical of the pharmaceutical industry. The gel-filled (diffusion) type electrodes offer the convenience of low maintenance and high stability, while the refillable liquid (flowing) type electrodes couple superior stability and accuracy.

Hamilton™ Sanitary pH Armatures

Normally the sensors in a bioreactor are mounted through the side of the reactor where they are exposed and vulnerable to accidental damage. To address this problem, the sensors are protected from mechanical damage and ambient moisture by rugged, but simple protection sleeves. Insertion and Retractable assemblies are available for a variety of sanitary connections, including 25mm ports and Tri-clamps.

Yokogawa SC24V Differential pH/ORP Sensor

The Model SC24V differential pH/ORP sensor is unique, offering maintenance free operation without any reference problems. The SC24V is designed for difficult applications where conventional sensors are ineffective. These include such measurements as brine solutions and applications as diverse as electrolysis processes and cheese manufacturing.

The differential measuring principle combines the normal potential generated by the pH glass with the potential from a Sodium pNa glass. In applications where Sodium-, Potasium- or Calcium-salt is present the glass will generate a stable reference voltage. The Cation Reference has NO junction, there is NO path from the process to the internal element; so NO poisoning can occur. Also since there is NO junction, there is NO plugging or coating problems to worry about and there is NO electrolyte depletion problem, because there is NO electrolyte.

This means the measurement can be done, eliminating problems caused by aging and pollution of the liquid junction, that are typically experienced with a conventional reference electrodes.

Yokogawa pH Analyzers

Yokogawa has been providing best-in-class analyzers for many years. The loop-powered FLXA21 features a robust NEMA 4x design, complete on-line (real-time) sensor diagnostics, easy auto-calibration, and HART®, FOUNDATION Fieldbus™, or PROFIBUS® communication options.

The EXAxt PH450 features even greater operation and application flexibility. The intuitive touchscreen interface with full language prompts allow for easy commissioning, calibration, troubleshooting, and access to stored data. Choose to display in five different languages or select the Trend Graph display for a graphical history of the process values.

Yokogawa Inductive Conductivity Sensors and Analyzers

The model ISC40 Inductive Conductivity sensor, seamlessly molded in FDA approved PEEK with USP class VI rating, has a wide measuring range of 1 to 2 million microSiemens. It is compatible with a variety of process adapters including Tri-Clamps, and the fact that it is immune from the effects of fouling, coating, and polarization makes the sensor virtually maintenance free.

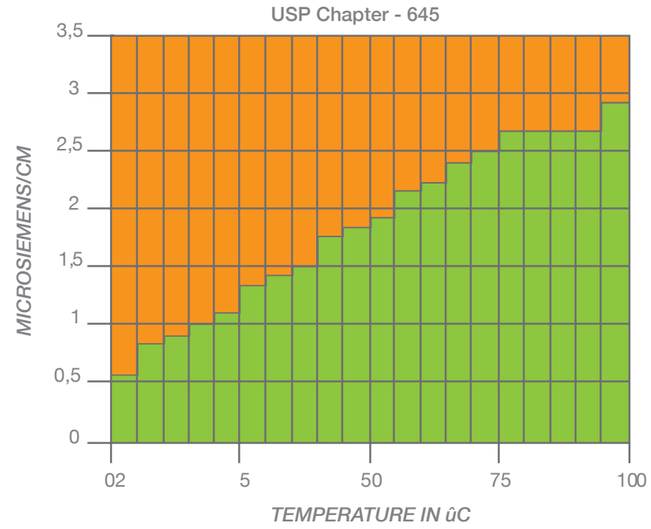
Yokogawa's Inductive Conductivity analyzers feature highly sophisticated compensation circuits that eliminate the measuring errors normally associated with inductive conductivity analyzers. Yokogawa's analyzers offer the highest accuracy and long-term stability in the market.

The model FLXA21 loop-powered analyzer has communication options ranging from HART®, FOUNDATION Fieldbus™, and PROFIBUS®. The model ISC450's intuitive touchscreen interface and multi-language capability provides easy, clear access to process, diagnostic, and trend graph data.

Yokogawa Contacting Conductivity Sensors and Analyzers

Whether used for measuring the purity of Water For Injection (WFI) or Clean In Place (CIP) processes, accurate and reliable conductivity measurements are critical in the Pharmaceutical industry. The best-in-class model FLXA21 loop-powered analyzer and the intuitive SC450 feature polarization and fouling diagnostics, pure water and electrolyte custom temperature compensation, as well as USP chapter 645 conductivity tables built-in.

The compact model SC4A conductivity sensors are designed to meet the demanding requirement of high purity water conductivity applications. The sensors are made of FDA approved materials, polished to pharmaceutical requirements, compatible with a variety of sanitary process connections, and have cell constants that are factory calibrated to three significant digits.



Hamilton™ Conductivity Sensors

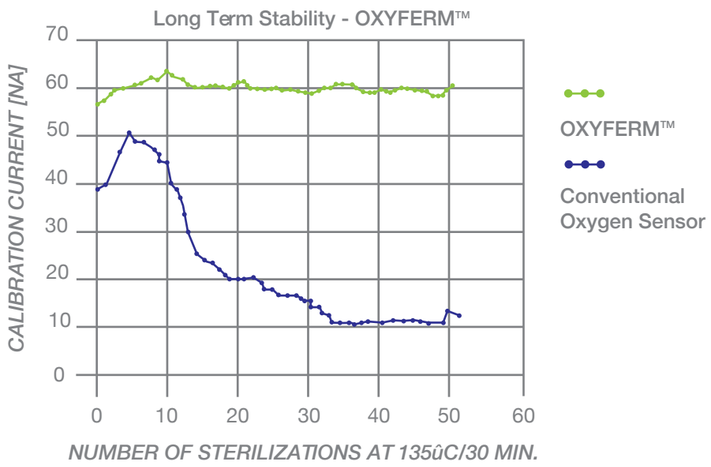
Hamilton's™ Conducell™ line of 4-Pole conductivity sensors feature open cell geometry that allows for a wide range of conductivity combined with a minimal footprint. The sensors are made of FDA approved material and are compatible with sanitary 25mm port or Tri-clamp process connections.

Hamilton™ Dissolved Oxygen Sensors

Dissolved Oxygen is one of the most important parameters controlled in the Pharmaceutical and Biotech industries today. Since their introduction in 1997, Hamilton's™ OXYFERM™ family of oxygen sensors has become a world leader because of the sensors' signal performance and low maintenance requirements.

The OXYFERM™ sensors are designed to withstand the harsh conditions present during process, sterilization, and cleaning. The 316 stainless steel body featues a membrane that combines the selectivity of TEFLON™, the permeability of Silicone, and the mechanical strength of stainless steel mesh. The membrane is pre-mounted in a stainless steel membrane cap that allows for safe and easy replacement of electrolyte or membrane in the infrequent instances when maintenance is needed. Armatures are available for sanitary 25mm ports as well as Tri-clamp process connections.

The performance of the OXYFERM™ sensor is unmatched in the industry. The design of the membrane allows a 90% response in a time of 30 to 60 seconds. The stabilization or polarization time of a newly installed sensor is typically less than 15 minutes. The design of the sensor negates effects of low rate and increases the life of the sensor. The graph illustrates the excellent performance of the sensor, even after 100 sterilizations without performing maintenance. Other types of oxygen sensors subjected to the same conditions require regeneration after 5 to 10 sterilization cycles.



Yokogawa Dissolved Oxygen Analyzers

Yokogawa can offer two flexible solutions to meet the dissolved oxygen analyzer requirements in the Pharmaceutical and Biotech industries.

The 115 VAC powered, model DO402G, features the flexibility of two 4-20 mA analog outputs as well as 4 programmable dry-contact alarms. The DO402G can display percent saturation, mg oxygen/l water and ppm DO.

The model FLXA21 is a 24VDC loop-powered analyzer. It has communication options ranging from HART®, FOUNDATION Fieldbus™, and PROFIBUS®. The FLXA21 offers automatic temperature compensation for both % saturations and ppm.

Both analyzers provide a simple-to-use "push button" user interface and feature compensation for temperature, atmospheric pressure and salinity to ensure the best measurement accuracy. The flexibility of the analyzers also allows compatibility with a number of dissolved oxygen sensors from many different manufacturers.

vigilantplant.®
The clear path to operational excellence

SEE CLEARLY | KNOW IN ADVANCE | ACT WITH AGILITY

VigilantPlant is Yokogawa's automation concept for safe, reliable, and profitable plant operations. VigilantPlant aims to enable an ongoing state of Operational Excellence where plant personnel are watchful and attentive, well-informed, and ready to take actions that optimize plant and business performance.

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Specifications Manual Literature

$890.00

HI5222 Research Grade pH/ISE/ORP Meter with CAL Check™

Qty: 1 Add to Cart

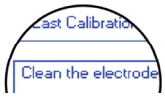
Be the first to review this product

Ships within 1-2 Business Days

The HI5222 is an advanced research grade dual channel benchtop pH/ISE/mV meter that is completely customizable with a large color LCD, capacitive touch keys, and USB port for computer connectivity. The HI5222 is rich in features including 5 point calibration, selectable resolution, data logging, alarm limits, comprehensive GLP, and many more while retaining simplicity in use with both dedicated key for routine operation and virtual keys that guide the user through setup options. The HI5522 ensures confidence in measurements with the exclusive Hanna Instruments CAL Check™ feature that alerts the user to potential problems during calibration including if the buffer is contaminated or the probe needs to be cleaned.

More Views

Capacitive touch keypad



ISE with choice of concentration units and incremental methods

CAL Check™

Details

The HI5222 is an advanced research grade benchtop pH/mV/ISE dual channel meter that is completely customizable with a large color LCD, capacitive touch keys, and USB port for computer connectivity.

The HI5222 features two galvanically isolated BNC connections for use with the expansive line of pH, ISE and ORP electrodes that Hanna Instruments offers. The meter is supplied with the HI1131B glass body, double junction, combination pH electrode that operates over a wide range of temperature from 0 to 100 oC. All readings are automatically compensated for temperature variations with the separate HI7662-T temperature probe that is included.

As a pH meter the HI5222 can be calibrated up to five points with eight pre-programmed buffers or five custom buffers. The HI5222 features Hanna's exclusive CAL Check™ to alert the user of potential problems during the pH calibration process. Indicators displayed during calibration include "Electrode Dirty/Broken" and "Buffer Contaminated." The overall probe condition based on the offset and slope characteristic of the electrode is displayed as a percentage after calibration is complete.

As an ISE meter the HI5222 can be calibrated up to five points with a choice of five fixed standards or five user defined in any concentration unit. The calibration data including date, time, standards used and slope can be viewed at any time along with the current measurement by selecting the Good Laboratory Practice (GLP) display option.

Three selectable logging modes are available: automatic, manual and AutoHold logging. Up to 100,000 data points per channel can be recorded in 100 lots, 50,000 records max/lot and exported to a computer for data review and storage.

Features at-a-glance

Highly Customizable User Interface – The user interface of the HI5222 allows the user to show measurements in various modes: basic measurement with or without GLP information, real-time graphing, and logging data. Calibration stability criteria can be adjusted from fast, moderate, and accurate. Programmable alarm limits can be set to inside or outside allowable limits.

Color Graphic LCD – The HI5222 features a color graphic LCD with on-screen help, graphic, and custom color configurations. The display allows for real-time graphing and the use of virtual keys provide for an intuitive user interface.

Capacitive Touch – The HI5222 features sensitive capacitive touch buttons for accurate keystrokes when navigating menus and screens. There are four dedicated keys that are used for routine operations including calibration and switching measurement modes and four virtual keys that change based upon use. The capacitive touch technology ensures the buttons never get clogged with sample residue.

Two Galvanically Isolated pH/ORP/ISE Channels – The HI5222 has two input channels that can be used for pH, ORP and ISE electrodes. Each input channel has connectors for BNC probes, reference probes and a temperature sensor. Each channel is galvanically isolated which means that two measurement probes can be in the same solution at the same time and the voltages produced will not interfere with each other.

Choice of Calibration – Automatic buffer recognition, semi automatic, and direct manual entry pH calibration options are available for calibrating up to five points, from a selection of eight standard buffers and up to five custom buffers.

GLP Data – HI5222 includes a GLP Feature thatallows users to view calibration data and calibration expiration information at the touch of a key. Calibration data include date, time, buffers used for calibration, and electrode offset and slope characteristics.

CAL Check™ – CAL Check™ alerts users to potential problems during the calibration of the pH electrode. Indicators include "Electrode Dirty/Broken," "Buffer Contaminated," electrode response timeand the overall probe condition as a percentage that is based on the offset and slope characteristics.

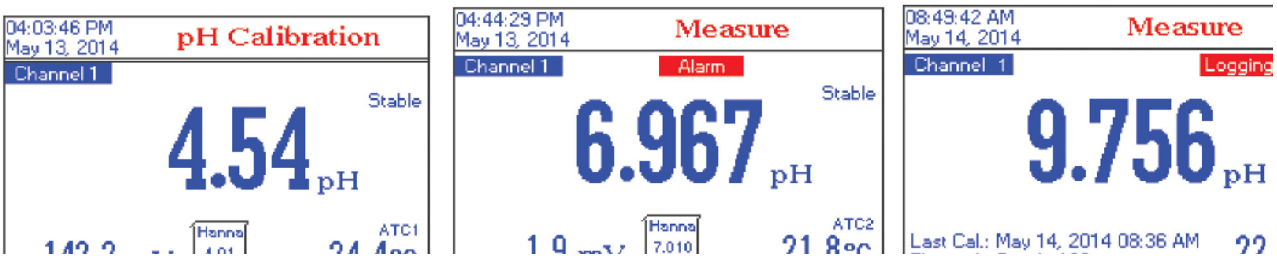
ISE Measurement with Choice of Concentration Units – The HI5222 allows for calibration and readings in choice of concentration units. The choices of concentration units include ppt, g/L, mg/mL, ppm, mg/L, µg/L, ppb, µg/L, mg/mL, M, mol/L, mmol/L, %w/v and a user-defined unit.

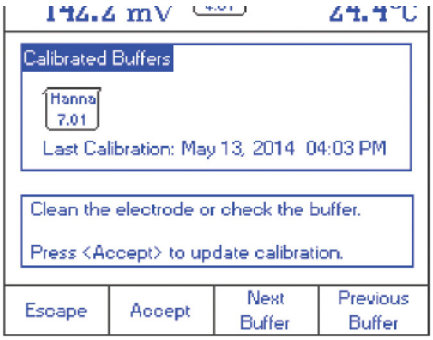
ISE Measurement with Incremental Methods – The known addition, known subtraction, analyte addition, and analyte subtraction incremental methods are pre-programmed into the HI5222. Simply follow the on screen guided procedure and the meter will perform the calculation automatically allowing for a higher level of accuracy to be obtained as compared to a direct ISE measurement.

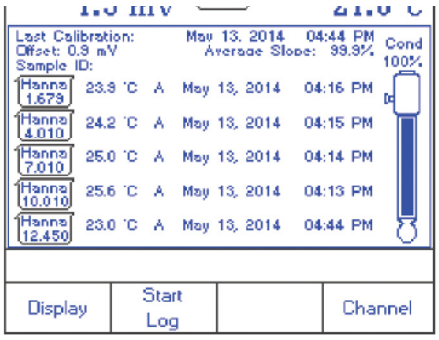
Data Logging – Three selectable logging modes are available on the HI5222: automatic, manual, and AutoHold logging. Automatic and manual logs up to 100 lots with 50,000 records max/lot with up to 100,000 total data points per channel. Automatic logging features the option to save data according to sampling period and interval.

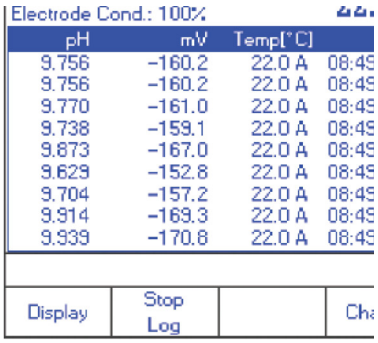
Data Transfer – Data can be transferred to a PC with the supplied USB cable and HI92000 software.

Contextual Help – Contextual help is always available through a dedicated "HELP" key. Clear tutorial messages and directions are available on-screen to quickly and easily guide users through setup and calibration. The help information displayed is relative to the setting/option being viewed.









CAL Check alert to potential problems during calibration

Comprehensive GLP Data

Real time logging

Specifications

pH Range	-2.000 to 20.000 pH
pH Resolution	0.1, 0.01, 0.001 pH
pH Accuracy (@25ºC/77ºF)	±0.1 pH, ±0.01 pH, ±0.002 pH ±1 LSD
pH Calibration	automatic, up to five point calibration, eight standard buffers available (1.68, 3.00, 4.01, 6.86, 7.01, 9.18, 10.01,12.45) and five custom buffers
pH Temperature Compensation	automatic or manual from -20.0 to 120.0 °C
mV Range	±2000 mV
mV Resolution	0.1 mV
mV Accuracy	±0.2 mV ±1 LSD
Relative mV Offset Range	±2000 mV

Temperature Range	-20.0 to 120.0 ºC, -4.0 to 248.0 °F, 253.15 to 393.15 K
Temperature Resolution	0.1 °C, 0.1 °F, 0.1 K
Temperature Accuracy	±0.2 °C, ±0.4 °F, ±0.2 K

ISE Range	1 x 10^{-6} to 9.99 x 10^{0} concentration
ISE Resolution	1; 0.1; 0.01; 0.001 concentration

ISE Accuracy @ 25 °C/77 °F	±0.5% (monovalent ions); ±1% (divalent ions)
ISE Calibration Points	automatic, up to five point calibration, five fixed standard solutions available (0.1, 1, 10, 100, 1000 choice of concentration) and five user defined units

Electrode/Probe	HI1131B glass body pH electrode with BNC connector and 1 m (3.3') cable (included)
Temperature Probe	HI7662-T stainless steel temperature probe with 1 m (3.3') cable (included)
GLP	calibration data including date, time, buffers used, offset and slope
Logging	record: 100,000 data point storage, 100 lots with 50,000 records/lot; interval: settable between 1 second and 180 minutes max log time; type: automatic, manual, AutoHold
Input Channels	2 - pH/ORP/ISE
Display	color graphic LCD with on-screen help, graphing, and custom color configuration
Connectivity	USB
Environment	0 to 50°C (32 to 122°F; 273 to 323 K), RH max 95% non-condensing
Power Supply	12 VDC adapter (included)
Dimensions	160 x 231 x 94 mm (6.3 x 9.1 x 3.7")
Weight	1.2 kg (2.64 lbs.)
Warranty	2 year limited warranty (meter), 6 month limited warranty (sensor)
Ordering Information	HI5222 is supplied with HI1131B pH electrode, HI7662-T temperature probe, HI76404W electrode holder, HI70004 pH 4.01 buffer solution sachet, HI70007 pH 7.01 buffer solution sachet, HI700601 electrode cleaning solution sachet (2), HI7082 3.5M KCl electrolyte solution (30 mL), 12 VDC adapter and instructions.

Compatible Products:

Check items to add to cart with the product on this page

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HI5004
pH
4.01
Technical

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HI5007
pH
7.01
Technical

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HI5010
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Calibration Buffer (500 mL)
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Calibration Buffer (500 mL)
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Calibration Buffer (500 mL)
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HI7004L pH 4.01 Calibration Solution (500 mL)
$14.00

HI7007L pH 7.01 Calibration Solution (500 mL)
$14.00

HI7010L pH 10.01 Calibration Solution (500 mL)
$14.00

HI70300L Electrode Storage Solution (500 mL)
$14.00

HI7061L General Purpose Cleaning Solution (500 mL)
$14.00

Related Literature & Media

HI5000 Series Benchtop Meters Brochure

Manual:

man5222_19_02_15_single

HI 2212

pH Benchtop Meter with Three Point Calibration

Get a Quote

- Up to three point pH calibration with five standard buffers or two custom
- GLP features
- Calibration expiration reminder
- Automatic Temperature Compensation

The HI 2212 is a pH and temperature benchtop meter.

Calibration can be performed at up to three-points using five standard and two custom buffers.

This instrument features manual or automatic temperature compensation with the HI 7662 temperature probe.

GLP (Good Laboratory Practice) feature provides data consistency. A calibration reminder can be set to alert the user, that too much time has elapsed since the last pH calibration and a new one should be performed.

Order Information:
HI 2212-01 (115V) and HI 2212-02 (230V) are supplied with HI 1131B pH electrode, HI 7662 temperature probe, HI 76404N electrode holder, HI 70004 pH 4.01 buffer solution sachet, HI 70007 pH 7.01 buffer solution sachet, HI 7071S electrolyte solution (30 mL), HI 700661 cleaning solution sachet, 12 VDC adapter and instructions.

Specifications | MSDS | Accessories | Downloads

Range	pH	–2.00 to 16.00 pH
	Temperature	–20.0 to 120.0 ºC (-4.0 to 248.0ºF)
Resolution	pH	0.01 pH
	Temperature	0.1 ºC
Accuracy	pH	±0.01 pH
	Temperature	±0.2ºC (excluding probe error)
pH Calibration		Up to 3 point calibration, 5 standard buffers available (4.01, 6.86, 7.01, 9.18, 10.01), and 2 custom buffers
Temperature Compensation		Manual or Automatic from -20 to 120ºC (-4.0 to 248.0ºF)
pH Probe		HI 1131B glass body pH electrode with BNC connector and 1 m (3.3') cable (included)
Temperature Probe		HI 7662 stainless steel temperature probe with 1 m (3.3') cable (included)
Input Impedance		10^{12} ohm
Power Supply		12 VDC adapter (included)
Environment		0 to 50°C (32 to 122°F); RH max 95%

Product Accessories

Electrodes

HI 1043B
Combination pH Electrode, Refillable w/ Double Junction
BNC Connection

HI 1053B
Combination pH Electrode, Refillable w/ Conical Tip
BNC Connection

HI 1083B
Combination pH Electrode w/ Micro Bulb
BNC Connection

HI 1131B
Refillable, Combination pH Electrode for the Laboratory and Beer Testing
BNC Connection

HI 1332B
pH Electrode for Chemicals, Quality Control, and Field
BNC Connection

Product Manuals
Manual: Download

Top Products

HI 98331
Soil Test™ Direct Soil EC Tester

HI 9125
Portable pH/ORP Meter

HI 98280
GPS Multiparameter Meter with

Dimensions	235 x 222 x 109 mm (9.2 x 8.7 x 4.3")
Weight	1.3 kg (2.9 lbs.)

Fast Tracker™ Tag Identification System

HI 98103
Checker® pH Tester